

European Commission

Evaluation of the European Medicines Agency

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Final report

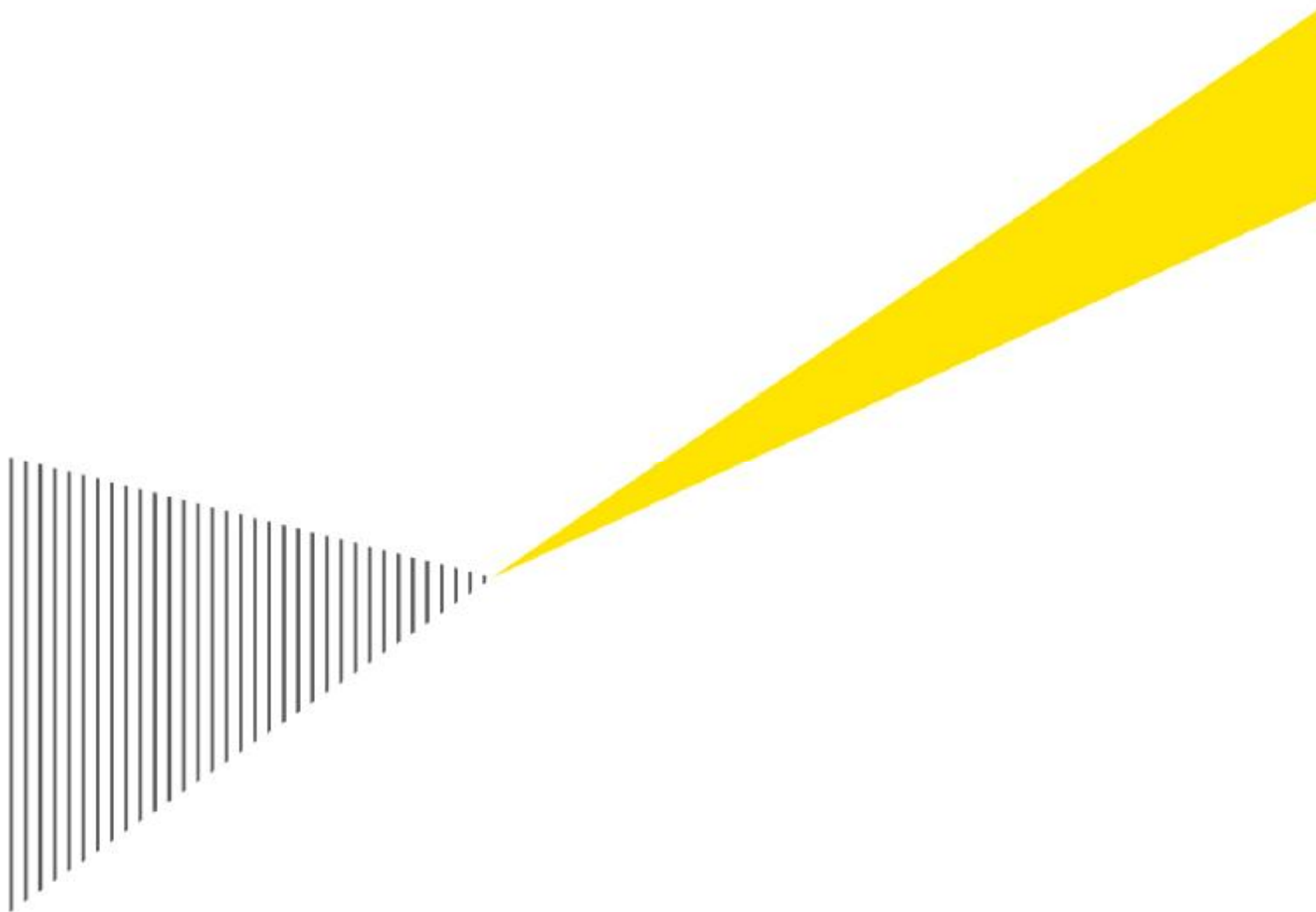


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List of abbreviations

ATMP	Advanced Therapy Medicinal Products
CAT	Committee for Advanced Therapies
CHMP	Committee for Medicinal Products for Human Use
CMD	Coordination Group for Mutual Recognition and Decentralised Procedures
COMP	Committee for Orphan diseases
CVMP	Committee for Medicinal Products for Veterinary Use
DCP	Decentralised procedure
EC	European Commission
EMA	European Medicines Agency (hereinafter as well referred to as “the Agency”) ¹
EU	European Union
FDA	Food and Drug Administration (US)
GCP	Good Clinical practices
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
HMA	Heads of Medicines Agencies
HMPC	Committee on Herbal Medicinal Products
HTA	Health Technology Assessment Bodies
ICH	International Conferences on Harmonisation
MAH	Market Authorisation Holder
MRA	Mutual-Recognition Agreement
MRP	Mutual-Recognition Procedure
NCA	National Competent Authorities (hereinafter as well referred to as national agencies)
OIE	World Organisation for Animal Health
SAG	Scientific Advisory Groups
PhV	Pharmacovigilance
PDCO	Paediatric Committee
VICH	Veterinary International Conferences on Harmonisation
WHO	World Health Organisation
WP	Working Parties

¹ The Agency has changed its corporate identity during the evaluation process. The abbreviation ‘EMA’ is no longer in use and replaced by ‘the Agency’ or ‘EMA’. This was not a consequence of any legislative change and does not have any impact on the Agency procedures.

1. Executive summary

Objectives and scope of the evaluation

Ernst & Young has been entrusted by the DG Enterprise and Industry to conduct the evaluation of the European Medicines Agency (EMA).² The evaluation process has been conducted between January and December 2009.

The evaluation objectives focus on the assessment of the effectiveness and the efficiency of the system dedicated to the provision of marketing authorisations for human and veterinary medicinal products fulfilling the basic requirements of quality, safety and efficacy. On the basis of the conclusions on the effectiveness and efficiency of the system, the evaluation addresses the contribution of the Agency to the protection of public and animal health, its contribution to the achievement of an operating internal market and the added value of the whole system for the stakeholders who are not directly involved in it (i.e. pricing and reimbursement national authorities, international and foreign agencies).

The evaluation has led to both strategic and operational recommendations to optimise the system and remove the possible barriers that prevent from an efficient and sustainable functioning of the Agency.

The focus of the present report is the centralised procedure; mutual recognition and decentralised procedures are in the scope of the study inasmuch as the Agency is affected by these procedures (support to CMD and arbitration procedures transmitted to CHMP/CVMP).

Approach, methods, tools and limits

The evaluation exercise has been organised in three phases: a first step focused on the setting up of an evaluation framework (definition of judgement criteria, indicators and related data collection tools for each evaluation question) and a detailed description of the whole system, followed by a second phase based on a large data collection taking into account all stakeholders and a third phase dedicated to data analyses, judgements and recommendations.

Primary data collection allowed to gather inputs from various types of stakeholders: EMA staff, NCAs experts, industry, patients' organisations and external stakeholders:

- Around 50 interviews have been conducted with EMA Secretariat staff, EU officials, Members of the European Parliament, pharmaceutical human and veterinary companies, patient and consumer organisations, US and Japanese competent authorities.
- A survey has been addressed to the National Competent Authorities aimed at gathering both concrete data on their involvement in the centralised authorisation system and their opinion of the added value of this involvement (40 out of 44 NCAs answered to the questionnaire).
- Six case studies at national level (UK, France, Sweden, Hungary, Portugal and Estonia) allowed an in depth analysis of the reciprocal impacts of the EU system on these NCAs. The Head of the agencies, the CHMP/CVMP members, and NCAs experts (internal or external) participating in assessment teams have been interviewed (47 people were met).
- Direct observation of EMA Committees (CHMP, Pharmacovigilance Working Parties) and CMDh meetings completed this data collection process.

² The EMA is understood as the combination of EMA Secretariat and the contribution of 44 National Competent Authorities.

Main limit of the evaluation is that hard data may lack in some evaluation fields. While the EMEA Secretariat provided with valuable and robust quantitative data related with its activities, it has been more difficult to gather data from NCAs on their involvement in EMEA procedures or data related to activities out of the scope of the EMEA Secretariat. It has been also difficult to obtain data on like the availability of authorised medicines in the Member States. The questionnaire to NCAs allowed to substantiate some statements; however quantitative data has not been filled in consistently by NCAs and therefore do not help sufficiently to provide a fair view on NCAs involvement in EMEA activities.

Key findings and recommendations are presented hereafter around seven main topics that emerged from most of performed analyses:

- ▶ Committees organisation,
- ▶ Involvement of NCAs in EMEA work,
- ▶ Role of EMEA Secretariat,
- ▶ Procedures,
- ▶ Communication,
- ▶ Industry fees,
- ▶ Telematics,
- ▶ Future challenges.

Committees organisation

The system for authorisation of human and veterinary medicines in the EU is mainly based on EMEA scientific committees assessing quality, safety and efficacy of centrally submitted products.

The present evaluation confirms the operational effectiveness of the system as a whole, which is recognised by all internal and external stakeholders. It provides with complete, clear and highly valued opinions within regulatory tight deadlines and allows the contribution of the best available experts in Europe, while ensuring the impartiality of the assessments. Whereas the scope of expertise covered by Member States (MS) representatives at the Committees may not be sufficient, the system encourages the contribution of NCAs experts, at various stages of the assessment process. Increased interactions between the stakeholders (between Member States representatives, but also with the applicants), either formal or informal, have been developed and participate in mutual understandings thus contributing in improving the quality of applications and assessment reports.

The effectiveness of the system has been maintained despite its growing complexity: the attractiveness of the centralised procedure together with the EU enlargement and the new regulations have led to an increased workload and an enlarged scope of responsibility for the EMEA over the past ten years. These changes have led to the creation of new committees (COMP, PDCO, CAT, HMPC) that required the implementation of additional procedures and new tools.

The **Committee for Orphan Medicinal Products** is generally considered a success, as it implemented effective incentives to promote development and marketing of medicinal products for orphan diseases. However, its sustainability may be put at stake both because the system may not appropriately compensate NCAs for their involvement, and because of potential evolutions, such as Personalised Medicine which could end up in significantly complicating the Orphan status designations procedures.

Paediatric regulation introduced new and stringent constraints on both the industry and EMEA resources. After a phase of adaptation, both stakeholders have seemed on their way to adapt to this evolution. However, from an operational and governance point of view, some concerns have raised on the status of PDCO vs. CHMP with respect to potential inconsistencies. Indeed, PDCO ability to make an opinion single-handedly on a Paediatric Investigation Plan (PIP) may eventually impact the availability of the drugs for children, as PDCO opinion on clinical plan may be put into question by the CHMP final opinion, given years later. PDCO may evolve therefore towards a Pre-committee model to reinforce consistency of the whole system.

However **the whole system is progressively attaining its maximum capacity**. The main opinion-making committees, CHMP and CVMP, are overwhelmed with work and their agendas could hardly be extended. The consistency between the 35 entities (Committees, WP, SAG, etc.) has been globally ensured by specific procedures and management tools, but some risks of overlapping and inconsistencies between these entities (PDCO / CHMP, CAT / CHMP WP, pharmacovigilance WP and CHMP) have been identified and may increase in the future. As a consequence of higher complexity, the external stakeholders fear the development of bureaucracy and rigidity.

Main recommendations in this area are focusing on systemic changes in the organisation, roles and responsibilities of the system. Priority is given to the adaptation of the governance and composition of the Committees, by taking into consideration both their political weight and technical inputs in the opinion making process. Some Committees may thus rather be composed by independent experts (PDCO, HMPC and CAT which decision are embedded to CHMP final validation) with more flexibility regarding the Member States representativeness prerequisite. CHMP and CVMP composition relevance will be all the more crucial as they are final opinion-making bodies: the management board may have the opportunities to select one candidate among several presented by each Member State. To overcome CHMP and CVMP workload issues, two dedicated committees may be created to deal with referrals and generics. In addition, working parties organisation should also be reviewed: some may be removed, others may be created according to their relevance with regards to the evolution of the scientific research and EMEA internal organisation.

Involvement of NCAs in EMEA work

The contribution of the NCAs to EMEA activities vary a lot from one NCA to another, depending mainly on their size, type of expertise and funding system. Seven Member States are taking 75% of CHMP Rapporteurships and Co-rapporteurships. Some efforts are being done to have a more balanced allocation of Rapporteurships between Member States, however the current appointment procedure still present scope for improvement in terms of transparency. Other types of work as peer reviews, guidelines and non-CHMP rapporteurships (PIP, Scientific advice, etc.) may also contribute to increase progressively contributions of other NCAs to EMEA activities.

All NCAs consider that their involvement in EMEA activities is of high scientific interest, benefiting also to national procedures. NCAs also benefit from electronic databases, interactions with the industry and personal relationships with European colleagues.

NCAs consider that their contribution to centralised authorisation system is covered by the compensation paid by the EMEA (50% of the fees paid by the industry), even if this compensation is barely considered as the unique incentive to take Rapporteurship. However, being part of EMEA network implies also important contributions to non-fee paid activities. NCAs involvement in such activities becomes all the more tricky that NCAs are facing an increasing lack of resources. Despite some differentiation based on their internal resources, such difficulties impact directly their level and type of involvement in EMEA activities. The whole compensation process is very complex and NCAs may have the feeling to be poorly compensated for referrals, paediatric investigation plan or orphan designation. **The funding system of non fee paid activities may be therefore clarified:** a realistic funding should be associated to each type of assessment activities, whether through fees, European or national funding. It is especially important as non-fee paid activities will increase in the near future (paediatric, orphan).

In this context, **the maintenance of the voluntary system still contains the flexibility required** and the great majority of NCAs do not plan to reconsider their involvement in EMEA activities, identified as a priority for national agencies.

Other recommendations have been identified to fully benefit from the resources of NCAs network: training programmes for NCAs experts may be reinforced, so as to enlarge the scope of experts able to deal with EU procedures; sharing the tasks on a specific procedure between several NCAs (and allow at the same time, the EMEA to pay directly the NCAs involved in a project assessment team) may be considered.

Role of EMEA Secretariat

The EMEA secretariat strongly contributes in the effectiveness of the system: it provides experts with administrative and regulatory assistance but also increases scientific assistance to the whole in specific fields (orphan, paediatric, etc.).

The operational efficiency of the whole system has improved over the period 2000-2008. The EMEA core activities have doubled (60 initial applications for human and veterinary medicines in 2000 to 119 initial applications in 2008) and the EMEA budget has followed the same trend, while assessment requirements have increased in complexity and EMEA scope of activities have strongly been extended. The increase in the workforce did not follow the increase of the activities in most of EMEA areas however the quality of the work has been maintained. With respect to specific tasks such as initial applications, orphan designation, post-authorisation activities and EMEA secretariat administrative support, some efficiency gains are obvious. However, fixed costs increased fourfold over the period whereas application costs only doubled, main contributing type of expenditure being data processing (maintenance of computer networks and equipment including telematics projects).

EMEA is in fact for 66% financed by fees paid by the industry. The European Commission subsidy is a balancing subsidy (around 20% of EMEA total budget which represented 194,4M€ in 2009) expected for some expenses for which an EC earmarked contribution comes in addition (Orphan, IT projects). The budget process thus allows the EMEA to cover its needs, but it is mainly depending on fee revenue which is susceptible to fluctuation fees fluctuation and requires therefore demanding planning exercises.

Considering EMEA secretariat key contribution to the authorisation system, few areas for further improvement have been identified. **The EMEA Secretariat has proved to be a learning organisation,**

identifying very early topics that require reflexion through working groups, discussion papers or action plans. EMEA Secretariat may also be careful not to increase too much formalism and administrative burden, notably in case of scientifically complex dossier requiring more time for assessment. In addition, particular attention should be paid to ensure the consistency of EMEA outputs with regards to the increasing complexity of EMEA organisation.

Procedures

The Centralised Procedure, EMEA guidelines and EMEA post-authorisation activities all are major contributions to the setting up of an effective European authorisation system, and thus contribute to the harmonisation of the internal market.

EMEA impact on harmonising the EU internal market is further enhanced by EMEA ability to provide services to the industry as streamlined as possible and in a fair, cost-appropriate and transparent manner.

Stakeholders generally recognize that EMEA continuously strives to improve both its timelines and its procedures. Timelines are continuously respected for the centralised procedure. The industry identifies little scope for improvement for some steps of the centralised procedures, especially with regards to the communication with the applicant (to be organised at the early stage of the process, through one single scientific entry point). The European Commission contributes also to the reliability and quality of the whole authorisation process, so that a very limited number of court cases related with EMEA opinions have been brought to the European Court of Justice since 2000.

Beyond its ability to promote medicines of major therapeutic interest, EMEA should also ensure that citizens are provided with the right level of safety. This is ensured both before and after marketing authorisation of products through **guidelines production and post-authorisation activities**.

EMEA guidelines are considered useful and valuable both by the industry, which can rely on them to enhance product development's predictability and by evaluators, who rely on them as a means to better ensure harmonisation of assessment practices.

Pharmacovigilance has received a lot of attention recently and is undergoing major changes through the preparation of a new legislation. Specific difficulties have been identified and somehow tackled at the data collection, storage and analysis level.

Scientific and regulatory advices also are major tools that can contribute to increase the predictability of evaluation outcomes for the industry. The steady increase of the number of applications to Scientific Advice is an indicator of this success. Industry representatives underline Scientific Advice use and quality, especially in helping them being better prepared and providing the right data. Both companies and NCAs have regretted the high level of formalism of Scientific Advice, which may in certain situations hinder the discussion. However, such formalism may also prove to be a guarantee of independence and transparency. The recent introduction of a new procedure for Scientific Advice has been welcomed, as it has helped reducing delays and simplifying the process, that proved to be a major hindrance for the industry.

Finally, major steps have been recently taken by the Commission to improve support to SMEs on the one hand, and increase generic products entry on the market on the other hand. These measures contribute to **enhance EU market harmonisation**. In particular the introduction of generic medicinal products into the Centralised procedure, have proved extremely efficient. This has resulted in a major increase of the number of centralised applications for generics, which now represent approximately half of the submissions. The ability of CHMP to answer to such an increase in workload is however put in question and requires organisational changes as suggested above.

On the veterinary medicinal products side, the introduction of generics has raised multiple issues. First, as in the case for other veterinary medicinal products, veterinary generic medicines generally do not go through the centralised procedure, but rather through DCP or MRP. However, generic veterinary products often result in referrals due to differences between Members States in the conditions of authorisation of the reference medicinal products in terms of withdrawal periods, posology, species etc.

Moreover, unnecessary delays and administrative procedures arise due to the obligation to re-assess eco-toxicity fully for veterinary medicinal products. As such an assessment is compulsory for each

equivalent reference product, it should not prove necessary to add such an additional evaluation, which both increases companies' administrative burden and CVMP workload.

At international level, all stakeholders recognise the quality of EMEA contribution in the harmonisation of authorisation procedures, as well as its efforts towards increased and better collaboration.

Within international organisations (ICH, VICH, WHO, OIE), EMEA has contributed and still contribute to the promotion of international standards through EMEA guidelines.

EMEA has developed very **strong relationships with the FDA**, leading to both formal and informal relationships (common technical working groups, monthly reports, staff exchange, parallel scientific advices, parallel designation of orphan medicines, permanent full-time employee hosting). A remaining area for harmonisation between FDA and EMEA has been suggested to be the clinical trial phases for which FDA performs centralised procedures whereas Europe processes through national agencies.

EMEA has also started cooperation with **other international medicine agencies** such as PMDA in Japan which is clearly highly supportive of such initiatives.³ Staff exchange remains an appreciated tool to develop cooperation.

EMEA is finally supporting **health authorities in developing countries** through issuing certificates of medicinal products and evaluating evaluation medicines intended for non-EU markets. Industry stakeholders are welcoming these efforts from the EMEA.

Communication

While EMEA generally has a very positive and increased impact on EU citizens, it generally suffers from a **lack of visibility**. Although EMEA communication strategy does make use of all the relevant channels (from specialised information like EPARs to more wide-reaching media such as the EMEA website), their impacts have remained limited. But EMEA communication strategy is heavily dependent on the network of NCAs, which are the local relays for EMEA information.

EMEA has recently put a lot of effort in order to improve its level of transparency, going beyond the legislation requirements. These efforts are recognized by the industry and other stakeholders. EMEA is also already considered by NCAs as setting the example in terms of transparency. This commitment does not go without a higher level of resource needs, and should be further strengthened by the recent proposal for a consistent Transparency Policy for EMEA.

An important type of stakeholders interested in EMEA outputs are the pricing and reimbursement bodies. Although scientific assessment performed by the EMEA and decision on the medicine reimbursement is not directly linked, EMEA outputs are recognised as a key step in a global process leading to pricing and reimbursement. In this respect, a fruitful cooperation has been established with Health Technologies Assessment and pricing and reimbursement bodies and there is a strong willingness to reach increased consistency within the whole drug evaluation and marketing process, especially through the improvement of EPAR to suit to HTA use,, but also through the collection and share of relative effectiveness data.

In a nutshell, the EMEA should pursue the work engaged on a differentiated communication strategy per target group: citizen, patients, consumers, healthcare professionals, veterinarians, academics, HTA, pricing and reimbursement bodies, etc.

Industry fees

By allowing, through the centralised procedure, a **relatively affordable marketing authorisation procedure**, EMEA offers the opportunity for global access to medicinal products for all citizens throughout the Member States.

³ Confidentiality arrangements are also signed with Canada and Australia.

The human pharmaceutical industry considers **EMEA fees to be fair and appropriate to the services provided**, with the notable exception of Scientific Advice, often considered as too expensive.

The veterinary pharmaceutical industry is more critical on EMEA fees rates, as the centralised procedure may prove less attractive because of more fragmented and nationally-specific markets. Also, MUMS medicines do not benefit from the same incentives as Orphan medicines do, and this is a limitation to the improvement of veterinary medicines coverage.

Independently of the fees level, EMEA fee structure is complex, as resulting from consecutive regulations. It may benefit from a simplification to lighten the administrative procedures, while keeping the fairness of fees as an important goal.

Telematics

Main issues identified within telematics were related with EudraVigilance. Although it is generally recognised that huge efforts have already been invested in the conception and realisation of EudraVigilance considered as the key tool of a coherent European Pharmacovigilance data management system, it remains a complex system to manipulate for the end-users with room for improvement. The new system will take into account some specific difficulties identified both at the data collection, storage and analysis level.

More generally, coordination between EMEA and NCAs may be reinforced in all IT-related projects, in order to facilitate the emergence of an European IT architecture, keeping the lead on harmonising pharmacovigilance procedures.

Future challenges

The EMEA as a part of the EU regulatory system has put **constant efforts** into adapting to scientific evolutions and ensuring that European citizens and animals, including specific populations, continue to be **provided with medicinal products of major therapeutic interest** that comply with the requirements of quality, safety and efficacy. The reliance on multiple specialized Scientific Advisory Groups, as well as the recent creation of three specialized committees are evidence of such efforts.

On a prospective point of view, **specific veterinary challenges** should be considered by clearly splitting human and veterinary subjects and considering them as independent fields, launching a reflection on the necessity for amending the veterinary regulation on specific aspects (eco-toxicity assessments, generics) together with a reflection on the appropriateness of market exclusivity or other incentives for MUMS products.

In addition, **potential impacts of recent scientific evolutions** on EMEA activities may be considered: middle-to-long-term impact of personalised medicine concepts (e.g. smaller and more well-defined patients population), on the need for specific competences at the CAT level to face the emergence of theranostics. The potential extension of the scope of EMEA activities should also be properly studied in the European framework with respect to clinical trials and medical devices to align with similar international organisations.

Conclusion

Since its creation in 1993, the EMEA has made considerable progress in maintaining an effective European authorisation system for human and veterinary medicinal products. In a quite limited timeframe, the EMEA has gained great consideration from all stakeholders, at European as well as at international level. EMEA opinions are undoubtedly considered of a very high quality from a scientific point of view and the Agency has become a leading actor in establishing international standards.

EMEA Secretariat together with 44 NCAs represents the archetype of an effective and efficient Community method. The organisation has gained in efficiency in the past years by maintaining the same level of quality. It allows also the contribution of the most relevant experts at various steps of the authorisation process. Although EMEA has proved to be a learning organisation, it is progressively reaching its maximum capacity. And communication remains an area of progress considering the increasing number of stakeholders concerned with different interests.

One may trust the EMEA to adapt to the coming new scientific or political challenges, if its organisation is appropriately altered in order to ensure the sustainability of the system.

With regards to its mandate, the EMEA has proved effective in protecting public and animal health by providing the EU citizens with human and veterinary medicinal products fulfilling the requirements for quality, safety and efficacy and has clearly contributed to the harmonisation of EU internal market for medicines. However, an important weakness of the European authorisation system has to be considered with regards to the impact on effective distribution of centrally authorised products. It appears that lot of these products are available only in a limited number of Member States. This is notably true for veterinary products.

A lot of stakeholders regret that medicines' distribution falls out of the EMEA scope.⁴ However, the industry provides already the EMEA with some data about the distribution of authorised products according to the so-called 'Sunset clause' (requirement for centrally authorised products to be placed on the European market within three years of the authorisation being granted)⁵. Monitoring such data with a look on the availability of authorised products in each Member State may allow the EMEA to identify main weaknesses of the system. This issue highlights an important challenge for the European authorisation system in the coming years: not only regarding the follow-up of distribution as a first step, but also through actions or incentives for broader distribution of authorised products in the Member States, thus contributing to optimise the impact of this system on the European public health. As pointed out in the first objective of the EC Communication on the future of the pharmaceutical sector, adopted on December 10th, 2008, this challenge may require political actions both at EU and Member States level: "options to improve the availability of medicinal products for patients in need, with a particular focus on smaller markets should be developed in close cooperation with Member States by 2010."

⁴ Although EMEA founding regulation outlined some responsibilities for the Agency in this area: "Furthermore, in order to create greater legal certainty it is necessary [...] to confer on the Agency powers to monitor the distribution of medicinal products authorised by the Community", Regulation (EC) No 726/2004, Considering 28)

⁵ Regulation (EC) No 726/2004, Article 14(4-6)

2. Introduction

2.1. Objectives of the evaluation

The present evaluation of the Agency focuses on the following main topics:

- ▶ The **effectiveness** of the system, i.e., the achievement of the objectives set forth by the regulation regarding the core objective of providing the EU citizens with human and veterinary medicinal products fulfilling the basic requirements of quality, safety and efficacy,
- ▶ The **operational efficiency** of the system, through an analysis of the cost / effectiveness ratio to answer the following question: could the objectives be achieved better with the same level of resources?
- ▶ On the basis of the conclusions on the effectiveness and efficiency of the system, the evaluation will address the following topics, inasmuch as possible:
 - The contribution of the Agency to the protection of public and animal health in light of its mandate,
 - The contribution of the Agency to the achievement of an operating internal market;
 - The added value of the system for the stakeholders who are not directly involved in it (i.e., pricing and reimbursement national authorities, international and foreign agencies).

The evaluation leads to both strategic and operational **recommendations** to optimise the system and remove the possible barriers that prevent the Agency from an efficient and sustainable functioning.

2.2. Scope of the evaluation

The scope of the evaluation has been precisely defined during by the kick off meeting in January 2009, i.e.:

- ▶ The centralised procedure is completely in the scope for the study.
- ▶ Pure national procedures are completely out of the scope for the study.
- ▶ Mutual recognition and decentralised procedures are in the scope for the study for as much as the Agency is affected by these procedures, i.e.:
 - When the Agency provides support to the CMD (Coordination Group for mutual recognition and decentralised procedures (human), CMD (h));
 - When these procedures lead to referrals, for which the Agency (CHMP) gives a recommendation to the Commission.
- ▶ Neither the internal organisation of the EMEA Secretariat itself nor telematics are the main issue of the evaluation exercise.

2.3. Content of the present report

This draft final report consists of the following parts:

- An executive summary of the evaluation objectives, scope, methodology, answers to evaluation questions and conclusion
- A reminder of the evaluation objectives and scope,
- The presentation of the research methodology and its limits,
- A synthetic description of the EMEA characteristics and functioning,
- The answers to the evaluation questions
- The organized and prioritized recommendations
- The conclusions of the evaluation study

Each evaluation question is introduced by an executive summary which provides with the main results of the analyses. The detailed answer per evaluation question is then developed according to the evaluation framework set up during the inception phase. Concrete recommendations are formulated throughout of the reasoning. Major recommendations are centralised under an organised and prioritised format in the dedicated recommendation section.

3. Research Methodology

3.1. Overview

The evaluation exercise started in January 2009. It was split into four main phases

Main steps	Main tasks	Deliverables	Submission
PHASE 1: Inception phase	Preliminary analyses Structuring	Inception report	05/03/2009
PHASE 2: Data collection and first analyses	Case studies / Surveys Interviews	Progress report	10/07/2009
PHASE 3: Analyses and opinion	Analyses and first answers to the evaluation questions	First findings and recommendations report	02/10/2009
PHASE 4: Final reporting phase	Final answers Conclusions and recommendations	Draft final report	17/11/2009
	Submission of the final report	Final report	January 2010

Table 1: Main phases of the evaluation exercise

Source: Ernst & Young, 2009

The results for each of these phases are described below.

3.2. The setting up of an evaluation framework

3.2.1. Four main steps

The evaluation process started with the creation of an evaluation framework.

1. Evaluation questions have been defined in accordance with the questions raised by the terms of reference
2. Sub questions have been created;
3. Several types of analyses have been proposed to answer each sub question. Related indicators and descriptors have also been defined.
4. For each indicator / descriptor, its source of information has been identified.

The establishment of an analytical approach per evaluation question was possible due to specific preliminary performed works:

- An in depth understanding of the functioning and the characteristics of the Agency and of the regulations to which it has to comply;
- A reconstruction of its intervention logic: what are the general, specific and operational objectives of the system as a whole

The final version of the inception report has been validated by the steering committee in April 2009.

3.2.2. Five evaluation questions

The evaluation process has been structured around five main evaluation questions, each of them referring to a general evaluation theme.

Main evaluation theme	Evaluation questions
A. Effectiveness	To what extent has the EMEA, as part of the European medicines network, contributed to an effective system of authorizing human and veterinary medicinal products for the EU?
B. Efficiency	To what extent has the EMEA, as part of the European medicines network, contributed to an efficient system of authorising human and veterinary medicinal products for the EU?
C. Long-term effectiveness on EU citizens	To what extent has the EMEA achieved its mandate to protect public and animal health by providing the EU citizens with human and veterinary medicinal products fulfilling the basic requirements for quality, safety and efficacy?
D. Impacts on the EU internal market	To what extent has the EMEA contributed to an effectively operating internal market for human and veterinary medicinal products?
E. Coordination and added value to other stakeholders	To what extent has the EMEA gained trust and provided added value to other stakeholders ?

Table 2: Evaluation questions

Source: Ernst & Young, 2009

The evaluation report is thus structured around detailed answers to these evaluation questions.

3.3. Data collection tools and results

3.3.1. Overview

A data collection plan was defined as part of the inception report.

The data collection started with the survey to the National Competent Authorities and ended in the beginning of October with interviews of specific stakeholders. The data collection plan as foreseen in the inception report has thus been respected

The following data collection tools have been used:

- Direct observation of EMEA Committees meetings,
- Survey to the National Competent Authorities,
- Interviews: EMEA Secretariat main stakeholders, pharmaceutical human and veterinary companies, patient and consumer organizations, US and Japanese competent authorities...
- Six case studies at national level allowing an in depth analysis of the impact of the EU system on the NCAs and vice versa.

Their implementation modalities, results and limits are presented below.

3.3.2. Direct observation

Tool description

Since most of the EMEA activities are related to Committees' work, the data collection plan included direct observation of some committees and working groups.

Attending a committee allowed us to have a better understanding of interactions between all stakeholders involved: Committee members, EMEA Secretariat, Industry representatives or other stakeholders. The role of the different committees, their internal functioning and related organisational issues were also easier to seize through direct observation.

Implementation modalities

The following Committees and working parties meetings were attended by the evaluation team:

- ▶ CHMP on 26/05/2009 and 23/06/2009,
- ▶ Pharmacovigilance Working parties on 26/05/2009,
- ▶ CMDh on 26/05/2009 and 23/06/2009.

Limits

By its nature, the direct observation is a collection tool that is limited to the scope of the observation (certain Committees meetings and dates).

However, following this first phase of data collection, some other Committees were identified as of important interest for similar direct observation: the CVMP, the PDCO and the Scientific Advice working party. These committees indeed follow different models compared to that of the CHMP.

Even though decentralised and Mutual Recognition Procedures are out of scope for the evaluation, attending the CMDh could bring some inputs in as to how much this Committee needs deal with referrals that may go to the CHMP in case of further arbitration.

3.3.3. Questionnaire to National Competent Authorities

Tool description

The questionnaire that was sent to the 45 NCAs participating in EMEA's network aimed to get a better understanding of the NCAs' expectations towards EMEA and their involvement in the Agency. This tool allowed us to qualify the perception of EMEA by the NCAs and to quantify their involvement in the European organisation.

The questionnaire covered six main items, from the NCAs' point of view:

- ▶ The National Competent Authority (NCA);
- ▶ The NCA's perception of the added value of EMEA;
- ▶ The NCA's resources;
- ▶ The NCA's involvement in EMEA's activities;
- ▶ The NCA's way of dealing with EMEA's activities;
- ▶ The NCA's opinion on the current organisation of EMEA.

The content of the questionnaire can be found in the appendix.

Implementation modalities

This questionnaire was designed following an interactive and iterative process:

- 1- 05/03/2009 - 27/03/2009: the questionnaire proposed in the inception report has been amended according to the revised version of the inception report;
- 2- 30/03/2009 - 17/04/2009: this new version has been tested with two NCAs, the Irish human and veterinary medicines' agency (IMB) and the French human medicines' agency (AFSSAPS);
- 3- 20/04/2009 - 06/05/2009: after integration of suggested improvements and simplifications, the questionnaire has been finalised and validated with members of the steering committee.

The final version of the questionnaire (see Appendix 7.1) was sent to all Heads of Medicines Agencies on May 7th with a return deadline of May 27th. With regards to the difficulties to provide quantitative data related to resources, additional information was sent to identify key questions more precisely and the deadline was postponed to June 17th.

40 responses were received which represent a return rate of 91% (44 targeted NCAs).

Limits

Some difficulties were identified in relation to the questionnaire: its length and also the quantitative questions could hinder complete responses from NCAs. That is why the deadline was postponed and further explanation was given to heads of medicines' agencies: they were offered the possibility of answering to a limited number of key questions, according to readily available information.

In order to obtain the highest return rate, a last reminder was sent by the European Commission on June 19th.

The limit of this tool is the fact that quantitative data had not been filled in by all NCAs, especially data related to budgets and number of procedures performed in the last three years. This lack has been mitigated by answers to qualitative questions, through case studies and through EMEA available data (regarding the number of procedures performed).

A specific issue was identified for non-remunerated activities. For non-remunerated activities, no quantitative data was available at NCA's level and also the questionnaire did not collect further information. As an alternative source we considered the on-going study on the new remuneration system, however since these outputs are not expected before the end of the year. Therefore some case studies with countries having time- and cost-tracking systems like the UK could bring helpful preliminary information.

3.3.4. Case studies

Tool description

Six case studies with the following objectives were implemented at national level:

- ▶ To conduct in depth analyses of the Member States level of involvement and EMEA impacts on NCA's human and veterinary activities;
- ▶ To observe and better understand the NCA's constraints and incentives towards the EMEA;
- ▶ To complete the data collected through the questionnaire (mainly quantitative) with qualitative data;
- ▶ To gather the opinion of the NCAs and their positions towards the future challenges;
- ▶ To provide inputs to the analyses conducted per evaluation question.

Field visits allowed meeting different kind of people within the NCA: the head of the agency, the members of CHMP and CVMP, and, internal or external experts participated in the assessment team.

Implementation modalities

The choice of the countries has been made taking into account several criteria such as NCA's level of involvement in EMEA, maturity of the NCA, level of activity in the pharmaceutical and veterinary domain, new / old Member States, large / small size of the Agency, etc.

The following countries were selected for the first phase of case studies:

- ▶ France,
- ▶ Sweden,
- ▶ United Kingdom.

In these three countries, 25 people have been interviewed in June.

After the July steering committee meeting and considering the answers received to the questionnaires, three other countries were visited:

- ▶ Portugal,

- ▶ Estonia
- ▶ Hungary.

In these three additional countries, 23 experts have been interviewed in early September.

Hereafter is presented an overview of the 10 visited NCAs and their main characteristics:

Country	Name	Scope	Mandate	Status	National funding system	Staff (2008)	Nr of interviewees
United Kingdom	MHRA	<ul style="list-style-type: none"> • Human medicines • Medical devices 	<ul style="list-style-type: none"> • Medicinal products evaluation • Delivery of authorisation decisions • Pharmacovigilance, • Inspections 	Ministry department	<ol style="list-style-type: none"> 1. National fees 2. Government funding 	1 002	6
United Kingdom	VMD	<ul style="list-style-type: none"> • Veterinary medicines 	<ul style="list-style-type: none"> • Medicinal products evaluation • Delivery of authorisation decisions • Pharmacovigilance, • Inspections • National legislation 	Ministry department	<ol style="list-style-type: none"> 1. National fees 2. Government funding 	149	4
France	AFSSAPS	<ul style="list-style-type: none"> • Human medicines • Medical devices • Cosmetics, Tattooing products, Biocides 	<ul style="list-style-type: none"> • Medicinal products evaluation • Delivery of authorisation decisions • Pharmacovigilance, • Inspections 	Independent public body	<ol style="list-style-type: none"> 1. National fees 2. Dedicated tax 3. Government funding 	1 025	2
France	ANMV	<ul style="list-style-type: none"> • Veterinary medicines 	<ul style="list-style-type: none"> • Medicinal products evaluation • Delivery of authorisation decisions • Pharmacovigilance, • Inspections • Research 	Independent public body	<ol style="list-style-type: none"> 1. Dedicated tax 2. Government funding 	90	6
Sweden	MPA	<ul style="list-style-type: none"> • Human medicines • Veterinary medicines • Medical devices • Cosmetics • Legal narcotics and pre-cursors 	<ul style="list-style-type: none"> • Medicinal products evaluation • Delivery of authorisation decisions • Pharmacovigilance, • Inspections • Health technology assessment 	Independent public body	<ol style="list-style-type: none"> 1. National fees 2. Government funding 	543	7
Hungary	OGYI	<ul style="list-style-type: none"> • Human medicines • Natural products 	<ul style="list-style-type: none"> • Medicinal products evaluation • Delivery of authorisation decisions • Pharmacovigilance, 	Subordinated to another institution	<ol style="list-style-type: none"> 1. National fees 2. Government funding 3. Publications 	231	5

Country	Name	Scope	Mandate	Status	National funding system	Staff (2008)	Nr of interviewees
			<ul style="list-style-type: none"> • Inspections • Pharmacopeia • Clinical trials 		4. Dedicated tax		
Hungary	OAI	<ul style="list-style-type: none"> • Veterinary medicines 	<ul style="list-style-type: none"> • Medicinal products evaluation • Delivery of authorisation decisions • Pharmacovigilance, • Inspections 	Subordinated to another institution	<ol style="list-style-type: none"> 1. Government funding 2. National fees 	58	5
Estonia	Ravimiamet	<ul style="list-style-type: none"> • Human medicines • Veterinary medicines • Medical devices 	<ul style="list-style-type: none"> • Medicinal products evaluation • Delivery of authorisation decisions • Pharmacovigilance, • Inspections • Health technology assessment 	Subordinated to another institution	<ol style="list-style-type: none"> 1. National fees 2. Government funding 	100	5
Portugal	Infarmed	<ul style="list-style-type: none"> • Human medicines • Medical devices • Cosmetics 	<ul style="list-style-type: none"> • Medicinal products evaluation • Delivery of authorisation decisions • Pharmacovigilance, • Inspections • Medicinal products reimbursement decisions 	Independent public body	<ol style="list-style-type: none"> 1. Dedicated tax 2. National fees 	327	4
Portugal	DGV	<ul style="list-style-type: none"> • Veterinary medicines 	<ul style="list-style-type: none"> • Medicinal products evaluation • Delivery of authorisation decisions • Pharmacovigilance, • Inspections 	Subordinated to another institution	<ol style="list-style-type: none"> 1. Government funding 	16	4

Table 3: Visited NCAs for case studies

Source: Ernst & Young, 2009

Limits

The advantage of case studies is that it provides the possibility to get a detailed understanding of the constraints and expectations of the visited Member States. It gives NCAs the possibility to come up with suggestions and to identify best practices that could be implemented at a broader level. However, on the contrary, only some of these elements can be directly generalised, as each Member State has its own specificities. A way to overcome this barrier slightly is to carefully analyze the countries balancing criteria such as NCA's level of involvement in EMEA, maturity of the NCA, level of activity in the pharmaceutical and veterinary domain.

Another limit of this case studies exercise lies in the willingness of agencies to disclose specific information.

Interviews were focused on the European system and the perception of the stakeholders, therefore no in depth analyses of the national procedures have been performed.

3.3.5. Interviews

Tool description

The main source for collecting information and for receiving the opinion from key stakeholders of the system were the interviews.. The following target groups were identified during the inception phase:

- ▶ EU officials,
- ▶ EMEA Secretariat staff,
- ▶ Industry (pharmaceutical companies and organisations),
- ▶ Patients' and consumers' organisations,
- ▶ Healthcare professionals' organisations,
- ▶ Health technology assessment and pricing bodies,
- ▶ Non-European organisations.

Interviews lasted between 1 and 2.5 hours. The interview guides can be found in Appendix (see paragraph 7.2).

Implementation modalities

The interviews have been conducted according to plan. The table below presents the performed interviews during the course of the study.

16 interviews have been conducted with the EMEA Secretariat. This is more than expected due to the fact that it appeared important to involve all key members of the EMEA Secretariat, since they are the core subject of the evaluation..

Regarding interviews with other stakeholders, 29 have been conducted. This represents more than 75% of the 38 initially targeted stakeholders. Difficulties have been encountered to reach some stakeholders from the industry, but in the end, the list of persons interviewed seems to be fairly representative for the stakeholders involved in the European authorisation system:

- EU officials (DG SANCO, DG Enterprises, DG Budget) and one member of the European Parliament,
- Pharmaceutical companies: 9 different type of companies
- Pharmaceutical industry representative organisations: 4 organisations representing different sectors (pharmaceuticals, generics, veterinary and SME),
- Patient and consumer organisations: 3 organisations,
- Healthcare professional organisations: 4 organisations,
- HTA and pricing organisation: 2 (EUnetHTA and ESIP),
- Non-European agencies: 2 (FDA, Japan),
- Other European agencies: 3 (ECDC, EFSA, EPO).

Target groups types	Target group selected for the data collection	Date of interview	
EU officials	EC officials: DG Budget	24/07/2009	
	Members of the European Parliament (2)	01/10/2009	
EMEA Secretariat	Quality of Medicines	30/06/2009	
	SME Office	04/05/2009	
	Communications and Networking	04/05/2009	
	Administration	04/05/2009	
	Personal and Budget	05/05/2009	
	Document management and publishing	05/05/2009	
	Accounting	05/05/2009	
	Executive support	05/05/2009	
	CIG	05/05/2009	
	IT	05/05/2009	
	Regulatory Affairs and Organisational Support	23/06/2009	
	Medical Information	23/06/2009	
	Pharmacovigilance and Risk Management	23/06/2009	
	Safety and Efficacy of Medicines	23/06/2009	
	Scientific Advice and Orphan Drugs	02/07/2009	
Executive direction	23/07/2009		
Pharmaceutical companies	GSK	30/07/2009	
	Pfizer	20/07/2009	
	- Human	Teva	27/07/2009
	- Veterinary	Hospira	12/06/2009

Target groups types	Target group selected for the data collection	Date of interview
	Elan	19/06/2009
	Shire	07/07/2009
	TopoTarget	07/09/2009
	Fort Dodge Animal Health	28/07/2009
	Merial	20/06/2009
	Ceva	07/07/2009
Pharmaceutical industry representative organisations	EFPIA (Pharma)	29/06/2009
	EGA (Generic)	17/07/2009
	- International IFAH (Veterinary)	03/06/2009
	- National LEEM	30/03/2009
Patient and consumer organisations	International Alliance of Patients' Organisations (IAPO)	01/07/2009
	European Organisation for Rare Diseases (EURORDIS)	07/07/2009
	BEUC	24/07/2009
Healthcare professional organisations	European Union of General Practitioners (JEMO)	20/08/2009
	European Federation of Nurses Association (EFN)	25/06/2009
	Federation of Veterinarians (FOV)	15/07/2009
	Pharmaceutical Group of the European Union (PGEU)	25/06/2009
National pricing and reimbursement authorities / Health technology assessment bodies	EUnet HTA	15/08/2009
	<i>ESIP</i>	14/10/2009
Non-European Agencies	FDA	09/09/2009
	Japan	23/07/2009
International organisations	ECDC	10/09/2009
	EFSA	03/09/2009
Comparable European Agency	EPO	14/09/2009

Table 4: List of interviews

Source: Ernst & Young, 2009

Limits

The data gathered through interviews is of high quality since the interviews were most of the time conducted with the relevant person within the institutions or the industries.

For some companies difficulties appeared in identifying and meeting the head of regulatory affairs. In the cases where we did not manage to reach the right person we identified some alternative companies with the same characteristics:

3.3.6. Secondary data collection

As part of our data collection plan, we have processed a full range of quantitative data.

As a general observation, Ernst & Young is welcoming the quality and robustness of the quantitative data related with EMEA activity. The EMEA played a leading role in the development of indicators to monitor their specific objectives: annual reports give a fair and documented overview of EMEA activity.

However, data related to the involvement of the Member States in EMEA activities have been more difficult to gather. Concerning the contribution of the Member States to each procedure, the EMEA has tracked the nationality of the contributors (Rapporteur, Co-rapporteur, coordinator, and peer-reviewer) to each procedure, which was not an easy task since the name of the contributor was the single entry point until recently. On the payment side, there are still fields of improvement in the EMEA reporting system, considering the difficulties to reconcile different EMEA databases.

Both the quantitative data and the qualitative data have been analysed. The qualitative data allowed us to perform a deep analysis and contributed largely to the diagnostic and recommendations. The choice which data to use depended on the on the evaluation question to answer, but both sources should lead to the same conclusion. The qualitative data mainly comes from the numerous questionnaires and interviews.

3.4. Analyses and approach followed per evaluation question

In order to answer the main evaluation questions (covering effectiveness, efficiency, long-term effectiveness, impacts on the EU internal market and the coordination and added value to other stakeholders), we have taken the following approach per question:

Effectiveness

To what extent has the EMEA, as a part of the European medicines network, contributed to an **effective system** of authorizing human and veterinary medicinal products for the EU?

The answers to this evaluation questions are structured around four main analyses.

- A1. Does the EMEA achieve its main objective, by providing the best possible scientific opinion for the centralised authorisation procedure?
- A2. Is EMEA contributing effectively to the harmonisation of authorisation decisions taken by Member States by resolving disagreement through arbitration procedures?
- A3. To what extent does the organisation of the Agency contribute or limit the achievement of these objectives?
- A4. To what extent does the EMEA organisation address the recent and future contextual challenges?

Efficiency

To what extent has the EMEA, as a part of the European medicines network, contributed to an efficient system of authorising human and veterinary medicinal products for the EU?

The answers to this evaluation questions are structured around four main analyses.

- B1. At what price have EMEA outputs and results been achieved?
- B2. Is EMEA resources allocation consistent with EMEA objectives and activity evolution?
- B3. Is the network of NCAs and experts efficiently mobilised?
- B4. Is EMEA using an accounting system allowing costs allocation and optimisation?

Long-term effectiveness on EU citizens

To what extent has the EMEA achieved its mandate to protect public and animal health by providing the EU citizens with human and veterinary medicinal products fulfilling the basic requirements for quality, safety and efficacy?

The answers to this evaluation questions are structured around five main analyses.

- C1. To what extent are EMEA evaluation activities contributing to the availability of high-quality, safe and effective medicinal products for EU citizens?

C2. To what extent is EMEA contributing to better information of EU patient and healthcare professionals aiming at the protection of public health?

C3. To what extent is EMEA supporting the development of medicinal products of major therapeutic interest?

C4. To what extent is the EMEA contributing to the efficiency of market surveillance (post-authorisation procedures) in the EU?

C5. To what extent is the EMEA contributing to the development of GMP and GCP in Europe?

Impacts on EU internal market

To what extent has the EMEA contributed to an effectively operating internal market for human and veterinary medicinal products?

The answers to this evaluation questions are structured around four main analyses.

D1. To what extent is the EMEA reducing timelines and administrative burdens for the entry on the market?

D2. To what extent is the EMEA contributing to the harmonisation of European marketing authorisation procedures?

D3. To what extent is the EMEA supporting innovation in the European pharmaceutical sector?

D4. To what extent is the EMEA supporting the entry of generic medicines in the market?

Coordination and added value to other stakeholders

To what extent has the EMEA gained trust and provided added value to other stakeholders?

The answers to this evaluation questions are structured around three main analyses.

E1. To what extent is the EMEA providing added value to pricing and reimbursement authorities?

E2. To what extent is the EMEA contributing to the harmonisation of authorisation procedures at the international level?

E3. To what extent is the EMEA supporting health authorities in developing countries?

4. Overview of the Agency characteristics and functioning

4.1. EMEA architecture

4.1.1. Global

The EMEA⁶ is the European Union body responsible for coordinating the existing scientific resources put at its disposal by Member States for the evaluations, and supervision of medicinal products. Its mission is to foster scientific excellence in the evaluation and supervision of medicines, for the benefit of human and animal health.

The EMEA therefore acts as the focal point of the European system, coordinating the scientific resources made available by NCAs.

The EMEA is headed by the **Executive Director** and has a **Secretariat** of approximately 530 staff members⁷ in 2009. The **Management Board** is the supervisory body of the EMEA, responsible, in particular, for budgetary matters. The Secretariat coordinates the pre- and post- authorisation evaluations and inspections.

Six **scientific committees**, mainly composed of members of all EU and EEA-EFTA countries, conduct the main scientific work of the Agency:

- ▶ Committee for Medicinal Products for Human Use (CHMP)
- ▶ Committee for Medicinal Products for Veterinary Use (CVMP)
- ▶ Committee for Orphan Medicinal Products (COMP)
- ▶ Committee on Herbal Medicinal Products (HMPC)
- ▶ Paediatric Committee (PDCO)
- ▶ Committee for Advanced Therapies (CAT)

A seventh committee, dealing with Pharmacovigilance, is currently in preparation.

Additional scientific work is conducted by working parties (WPs) and scientific advisory groups (SAGs). These are also mainly composed of members of all EU and EEA-EFTA states. WPs are mainly involved in the development of guidelines on the matters they are expert on. SAGs, on the other hand, provide expertise support to the committees on specific topics and in particular therapeutic areas.

The Agency also brings together the scientific resources of some **44 national competent authorities** in 30 EU and EEA-EFTA countries in a network of over **4,500 European experts** (source: EMEA website),

⁶ The European Medicines Agency launched a new visual identity on 8 December 2009. As part of this, use of the abbreviation 'EMEA' was discontinued. The abbreviation is now replaced with 'the Agency' or 'EMA'. Please note, that the change to the new visual identity had no consequence on the scope of responsibilities of the Agency.

⁷ Authorised temporary agents

participating in the work of the EMEA as members of the scientific committees, working parties, scientific advisory groups etc..

In 2008, the EMEA structure was organised as follows:

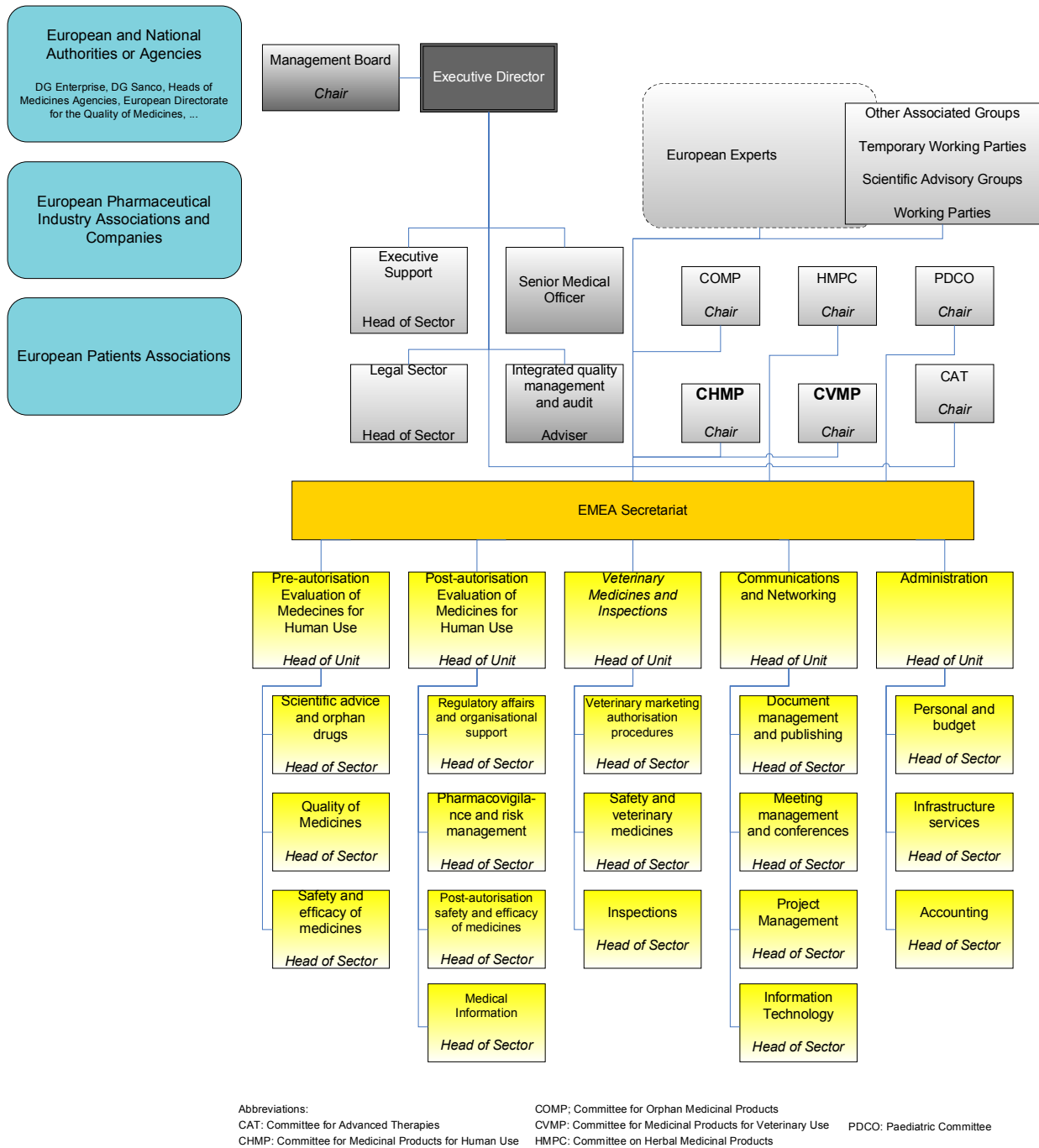


Figure 1: EMEA architecture in 2008

Source: Ernst & Young, 2009

4.1.2. The Secretariat and Management Board

As said before, the EMEA is headed by an Executive Director and has a Secretariat of approximately 530 staff members in 2009 (see Figure 2 for EMEA Secretariat Staff evolution since 2001). The Management Board has a governance role in the EMEA and is particularly involved in the budget's matters.

Members of the Management Board are appointed by Member States, the European Commission, the European Parliament and the Council⁸ for a term of three years, which may be renewed. Members are appointed on the basis of their relevant management experience and experience in human or veterinary medicines. Members are also appointed in order to guarantee the highest level of specialist qualifications, broad spectrum of relevant expertise and the broadest geographical spread within the EU.

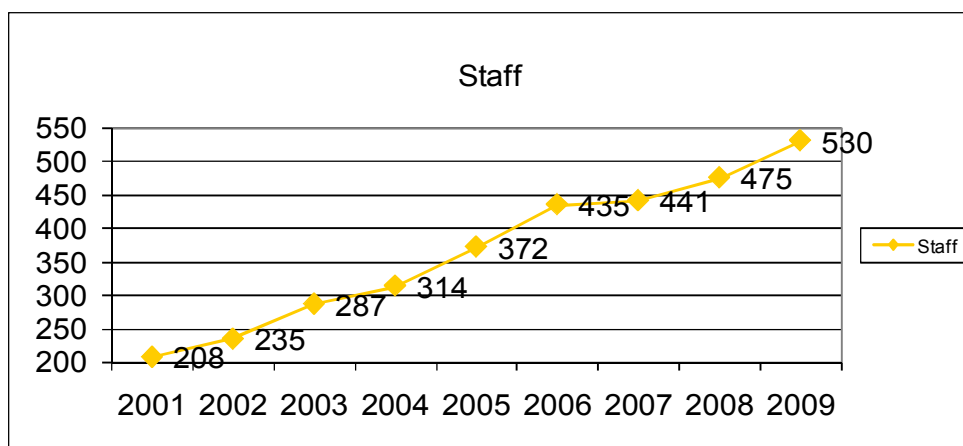


Figure 2: EMEA Secretariat staff evolution after 2001

Source: EMEA annual reports (2001, 2002, 2003, 2004, 2005, 2006, 2007, 2008 and 2009)

4.1.3. Six committees and their support structures

Scientific Committee members (and, where relevant, alternates) are appointed by Member States for a term of three years, which may be renewed. The Management Board is consulted on appointments before the appointment of CHMP and CVMP members. Such members shall be chosen given their role and experience in the evaluation of medicinal products for human and veterinary use, as appropriate, and shall represent their respective NCAs.

It should be noted that the European Commission appoints some COMP members. Moreover, at the level of the CHMP, CVMP and HMPC, the Committee may decide to appoint co-opted members.

All Scientific Committees may give their scientific opinions or recommendations only when two thirds of the total members of the Committee eligible to vote are present. Whenever possible, a decision shall be taken by consensus. If such consensus cannot be reached, the names of the members expressing the divergent positions shall be mentioned in the minutes along with their positions. In the event that no absolute majority (i.e., favourable votes by at least half of the total number of Committee members eligible to vote plus one, noted that the votes of the EEA-EFTA States are counted separately) is found for the decision, the opinion is considered as negative.

A description is attached of each Committee according to the relevant regulation and rules of procedure, presenting the respective:

- Key applicable regulations and directives;

⁸ The Council appoints has no direct representative but appoints 4 civil society representatives: 2 patients', 1 doctors' and 1 veterinarians' representatives.

- Roles and responsibilities;
- Structure.

As per the regulation (EC) No 726/2004, the committees may refer to working parties or scientific advisory groups.

Working Parties

As part of their assignment, experts can contribute to a Working Party (WP). The creation of a WP may be initiated by the CHMP, CVMP, COMP and HMPC according to the regulation (EC) No 726/2004.

Each Scientific Committee shall establish its own rules of procedure in relation to its working parties. In general, they set up a number of WP at the beginning of each three-year mandate.

A WP is established to provide recommendations on the matters it is expert on: scientific support to evaluation in coordination with the Rapporteur and Co-rapporteur (if any), development of guidelines...

The WP complies with the respect of the fair dissemination of information among Member States: each member of the Committee is generally invited to appoint one expert of its own state, or may appoint a contact person with specific expertise to attend meetings. The final composition is agreed by the related committee. An expert may belong to various WPs.

Each appointed contact person shall participate actively in the work of that WP and regularly attend its entire meetings.

Whenever work of a temporary or ad hoc nature is required, the committees may establish a temporary WP to conduct it. The work of these parties generally involves the preparation of proposals on a specific scientific topic, the preparation of responses to specific questions raised by the corresponding committee and the drafting or revision of guidelines relating to the scientific field in which the temporary WP has special competence.

Scientific Advisory Groups

A Scientific Advisory Group (SAG) is generally composed of a core group appointed for 3 years, who shall be proposed by CHMP/the EMEA, and should as far as possible reflect various “schools of thinking” or EU therapeutic practices. Additional experts, interested parties (patients/healthcare professionals) may be invited on case-by-case basis according to the expertise required by the related Committee, in coordination with the Rapporteur, or with the Rapporteur and EMEA Secretariat, if the adequate expert were originally not in the EMEA database. Company representatives may also be invited to answer questions of SAGs.

SAG may be convened at the request of a Committee to provide independent recommendations on scientific/technical matters in connection with the evaluation of specific types of medicinal products or treatments.

Scientific Advice Working Parties

The Scientific Advice Working Party (SAWP) has the particularity to be a multidisciplinary group set up by the CHMP with wide scientific expertise in preclinical safety, pharmacokinetics, statistics and specialist fields (including cardiology, oncology, diabetes, neurodegenerative disorders and infectious diseases).

Its role is mainly to provide to the Applicant scientific advice for medicinal products for human use and protocol assistance for orphan medicinal products. It shall provide the Applicant with an integrated view with regards to quality, pre-clinical and clinical safety (pharmacovigilance and risk/minimisation aspects) and efficacy.

It is composed of 23 members appointed by the CHMP (among either CHMP members or European experts) and 3 members appointed by the COMP.

Another Scientific Advice Working Party (SAWP-V) has been established by the CVMP. The SAWP-V is an equivalent of the human SAWP and provides scientific advice to applicants.

4.1.4. 4500 experts network

The Agency is coordinating a network of over 4,500 European experts from the NCAs of the 27 European Union Member States and the 3 EEA-EFTA States (Iceland, Liechtenstein and Norway).

Member States shall provide the EMEA with a list of experts, with proven experience in the evaluation of medicinal products in order to serve as permanent members of WP or SAG, or to act as additional experts to scientific committees, WP or SAGs. Appointments by Member States should be accompanied by a description of the experts' qualifications and their specific areas of expertise.

In addition, situations may arise where the need for additional expertise, not covered by appointments by Member States, is identified at the level of the scientific committees. In such circumstances, the appointment of the identified expertise is carried out by the EMEA.

The experts are providing services on the basis of a contract between the NCA and the EMEA.

Experts (as for any appointed person working for the EMEA) must work independently from any parties external to the EMEA. Their scientific competence shall be guaranteed by their appointing authority while their independence and integrity shall be assured through annual public declaration of interests. More generally, the EMEA has established a formal procedure and appointed a dedicated structure to assess whether the members and experts are allowed to participate to EMEA activities.

4.1.5. The external environment

The EMEA is articulating its activities within an environment with many stakeholders e.g.: pharmaceutical companies, healthcare professionals, European and national authorities, patients ...

The Heads of Medicines Agencies (HMA) who are representing all the Member States Competent Authorities are working closely with the EMEA. The HMA has the leadership during the mutualised procedure for authorisation of medicinal products through the Co-ordination Group for Mutual Recognition and Decentralised Procedures (CMD).

By its role and activity, the EMEA obviously interacts with the pharmaceutical industry. The EMEA is providing support to these stakeholders by implementing Best Practice Guide for example. Another initiative among others is the recent workshop organised between the EMEA and the European Federation of Pharmaceutical Industries and Associations on biomarkers.

The EMEA may also enhance its interaction with other stakeholders by implementing a formal framework through the creation of WP, as it is already the case with the Working Party with Healthcare Professional Organisations or Working Party with Patient and Consumer Organisations.

Finally, the EMEA contributes to the European Union's international activities through its work with the European Pharmacopoeia, the World Health Organisation, the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Products (VICH) among other international organisations and initiatives.

4.2. Process map

Beside its operational activities, the EMEA defines its strategy, business plan and work priorities. It also obviously defines and manages the infrastructure and work environment needed to the accomplishment of its mission. They are represented in the chart below.



Figure 3: EMEA process map

Source: Ernst & Young, 2009

The three operational activities highlighted in the diagram will be described in further detail hereafter.

4.2.1. Scientific opinion

The EMEA primarily gives its opinion on marketing authorisation applications. Medicinal products can be authorised in the European Union through the centralised, mutual recognition or decentralised procedures. The EMEA is directly involved in the centralised procedure or in case of dispute arising from the two other procedures (referrals arising from the decentralised and mutual recognition procedures).

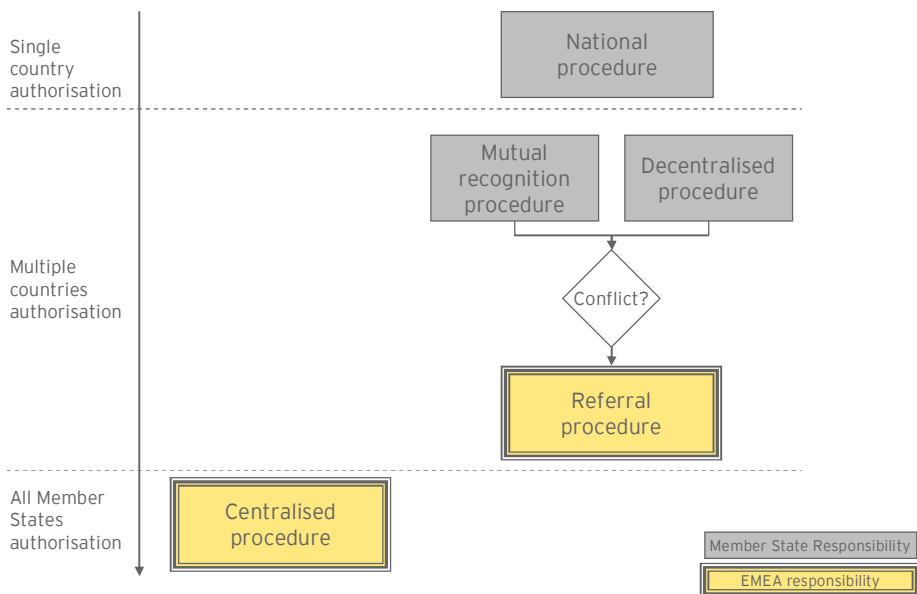


Figure 4: Authorisation procedures

Source: Ernst & Young, 2009

Centralised authorisation procedure

Except for their respective scopes, centralised procedures to approve veterinary or human medicinal products are pretty similar. For the sake of the conciseness of the report, the human medicinal products will be mainly addressed.

Scope

The Agency (EMA) is responsible for the centralised procedure. This procedure results in a single marketing authorisation (called a 'Community marketing authorisation') that is valid across the European Union, as well as in the EEA-EFTA States. The centralised procedure is **compulsory** for medicines that are:

- ▶ derived from biotechnology processes, such as genetic engineering;
- ▶ medicinal products for human use intended for the treatment of HIV/Aids, cancer, diabetes, neurodegenerative disorders or autoimmune diseases and other immune dysfunctions;
- ▶ medicinal products deemed as 'orphan medicinal products' (medicinal products used for rare diseases)
- ▶ medicinal products for veterinary use intended primarily for use as performance enhancers in order to promote the growth of treated animals or to increase yields from treated animals.

For medicines that do not fall within these categories (the 'mandatory scope'), companies have the **option** to submit an application for a centralised marketing authorisation to the EMA. This is allowed as long as the medicine concerned is a significant therapeutic, scientific or technical innovation, or if its authorisation would be in the interest of public health.

Applications through the centralised procedure are submitted to the EMA. Evaluation by the Agency's relevant committee (CHMP or CVMP) takes up to 210 days, at the end of which the relevant committee adopts an opinion on whether the medicinal product should be authorised or not. This opinion is then communicated to the European Commission, which has the ultimate authority for making decisions on marketing authorisations in the EU.

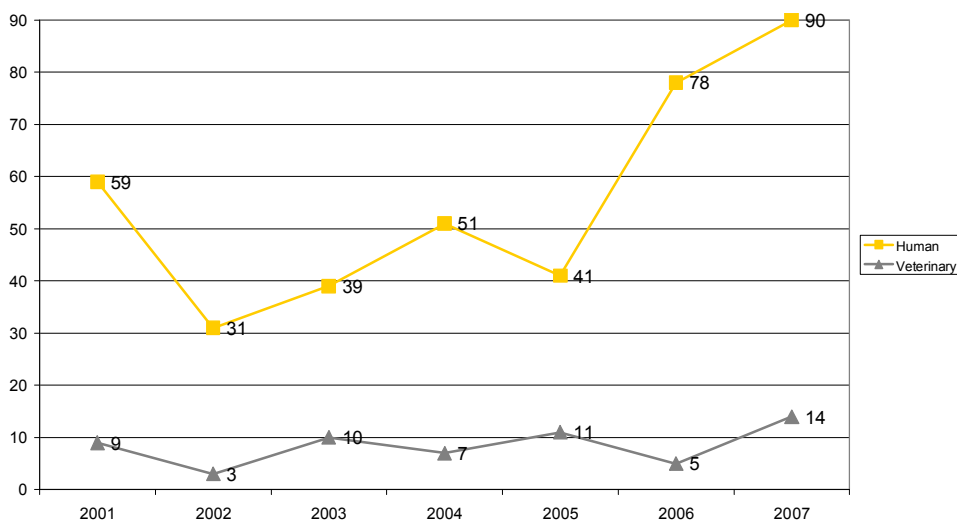


Figure 5: New application evolution since 2001

Source: EMEA annual reports (2001, 2002, 2003, 2004, 2005, 2006, 2007, and 2008)

Referral Procedure

Outside the mandatory scope of the centralised procedure, there are two possible routes available to companies to receive authorisation of their products in several countries simultaneously:

- ▶ Using the **decentralised procedure**, companies may apply for simultaneous authorisations in more than one EU country of medicinal products that have not yet been authorised in any EU country and that do not fall within the mandatory scope of the centralised procedure. This decentralised procedure takes 210 days if there is no dispute between the states.
- ▶ In the **mutual-recognition procedure**, a medicinal product is first authorised in one EU Member State, the so-called Reference Member State, in accordance with the national procedure of that country. Then, further marketing authorisations are sought from other EU countries using this procedure whereby the countries concerned agree to recognise the validity of the first, national marketing authorisation. This procedure takes 90 days if there is no dispute between the states

Disputes arising in the course of these procedures are referred to the Co-ordination group for Mutual Recognition and Decentralised Procedures (CMD(h) for human medicines, or CMD(v) for veterinary products).

The CMDs depends on the Heads of Medicines Agencies (HMA), however their secretariat is managed by the EMEA. The CMD(h) shall make its best efforts to reach to an agreement on the action to be taken within 60 days as from the disagreement. Failing to do so, the matter is transmitted to the CHMP or CVMP as applicable.

Scope

The community referral procedure occurs when CMD has not reached an agreement on disputes arising from decentralised and mutual-recognition procedures. It is used for the following reasons:

▶ Case 1

Arbitration procedures (either under Article 29 of Directive 2001/83/EC as amended or Articles 6(12) and 6(13) of Commission Regulation (EC) No 1084/2003) are initiated because of disagreement between the Member States or because of a disagreement of the marketing-authorisation holder with the Member States in the framework of the mutual-recognition or decentralised procedures.

▶ Case 2

Article 31 and 36 referral procedures are mainly initiated in case of Community interest and generally for safety-related issues.

▶ Case 3

Article 30 referrals are mainly initiated in order to obtain harmonisation of authorisations for medicinal products authorised in the Community by the Member States.

▶ Case 4

Article 107 procedures under Directive 2001/83/EC, as amended, are initiated to obtain a CHMP/CVMP opinion further to the suspension or withdrawal of the marketing authorisation of a medicinal product in a Member State as a result of pharmacovigilance data.

▶ Case 5

Article 5(3) procedures under Regulation (EC) No 726/2004 require a CHMP/CVMP opinion on any scientific matter raised by the EMEA, the European Commission or a Member State.

Figure 6 shows the evolution of referrals and their origin since 2001. This graph reveals the strong increase of such procedures in the last few years, which could lead to a saturation of EMEA dedicated resources.

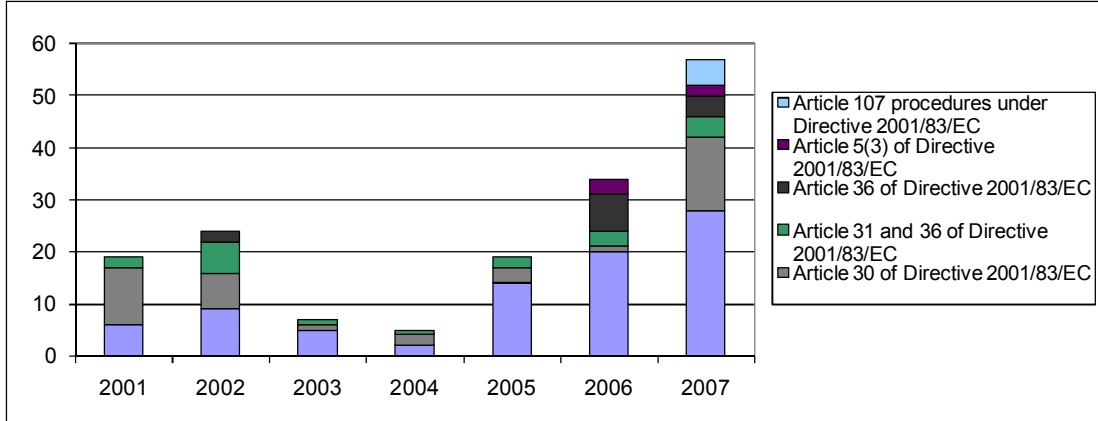


Figure 6: Arbitration and Community referrals since 2001

Source: EMEA annual reports (2001, 2002, 2003, 2004, 2005, 2006, 2007, and 2008)

National authorisation procedures

Each EU Member State has its own procedures for authorisation (within its own territory) of medicinal products that fall outside the scope of the centralised procedure. Information about these national procedures can normally be found on the website of the National Competent Authority in the country concerned. When a Member State is the first country to authorize a medicinal product, it is referred as the Reference Member State.

Focus on the actors

The actors involved in the centralised procedure for medicinal products are represented in the following diagram:

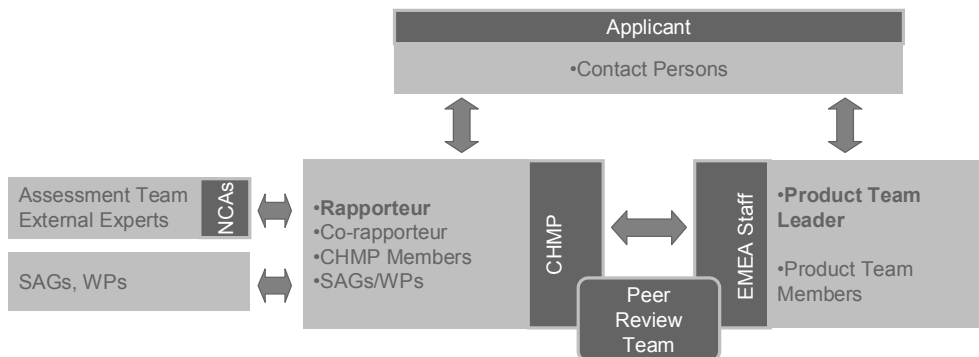


Figure 7: Rapporteur versus Product Team Leader

Source: EMEA CHMP Rules of Procedures (EMEA/45110/2007)

Product Team Leader and Product Team Member

The need for the appointment of a Product Team Leader and Product Team Members can be identified:

- ▶ when the Applicant requests a pre-submission meeting;
- ▶ when the Applicant requests the appointment of a (Co)- Rapporteur;
- ▶ or when the eligibility to the Centralised Procedure is confirmed.

The Central Information Group Secretaries then request the appointment of the Product Team Leader by the Head of Sector Quality of Medicines, and the Head of Sector Safety & Efficacy. The Product Team Leader is the main contact point during the procedure and is responsible for providing the product team with regular feedback on the progress of the application. In case of any issues, he/she may organise internal meetings to find a solution.

Depending on the questions from the Applicant, Product Team Members are appointed by the inspection department, the scientific advice and orphan drugs departments, regulatory affairs, risk management or from any other department as deemed necessary.

CHMP Rapporteur/Co-Rapporteur and their assessment teams

When scientific evaluation is necessary with regards to a given procedure, a Rapporteur, and if relevant a Co-Rapporteur, are appointed amongst the members of the CHMP (including co-opted members) or CHMP's alternate members.

The Rapporteur/Co-Rapporteur is assisted by a team of assessors and experts (assessment team) during the various phases of the assessment of the application. This team of experts is appointed by the Rapporteur from a list held by the EMEA to assist in the assessment of applications. The Co-Rapporteur may also appoint a team of assessors/experts in the same way, with a view to challenging the work of the Rapporteur.

The involvement of the Co-Rapporteur is mandatory with regards to:

- ▶ the centralised pre-authorisation phase;
- ▶ the assessment of a Type II variation application concerning new indication(s);
- ▶ renewals of centrally authorised medicinal products and;
- ▶ referral procedures.

The involvement of the Co-Rapporteur in other variations/post-authorisation procedures is determined by the CHMP on a case-by-case basis.

The role of the Rapporteur as well as the Co-Rapporteur is mainly to:

- Be in charge of the scientific assessment/evaluation undertaken by the team with regards to the quality, efficacy and safety related aspects of the medicinal product in accordance to the timeframes provided by the European Union framework
- Coordinate the inputs from the assessment team;
- Coordinate input from other various stakeholders, mainly Working Parties, Ad Hoc Expert Groups, SAGs;
- Identify post-authorisation measures to ensure and monitor the safe and effective use of the medicinal product after authorisation, and involve additional expertise as considered necessary for this matter;
- Act as the CHMP representative/spokesman in liaison with the Applicant/MAH;

- Interact in the best possible way with the EMEA/Product Team Leader/Product Team Members;
- Ensure that all her/his activities are performed in a transparent manner and inform accordingly the EMEA Secretariat.

The assessment team will use its scientific competence and regulatory experience to provide cross sectoral expertise support to the Rapporteur.

Peer Review Team

Peer review takes place during the initial phase of the assessment of new marketing authorisation applications, and in particular in the period between the release of the (Co)-Rapporteurs' initial assessment report and the adoption of the CHMP list of questions (day 120). It aims at improving the quality of the (Co)-Rapporteurs' assessment reports. This process consists of reviewing the (Co)-Rapporteurs scientific evaluation, as well as reviewing the validity of the scientific/regulatory conclusions reached, by other members of the CHMP.

Generally the peer review team is composed of CHMP members (including co-opted members) or CHMP alternate members. The peer review is mainly coordinated by the Product Team Leader and, as applicable, Product Team Members.

4.2.2. Pharmacovigilance

Another significant activity of the EMEA is Pharmacovigilance. Pharmacovigilance, both for human and veterinary products, is part of the EMEA post-authorisation activities. Pharmacovigilance includes all activities relating to the detection, assessment and prevention of adverse effects of medicinal products. However, not all these activities are the responsibility of the EMEA, a lot remains under the responsibility of the Member States.

EMEA pharmacovigilance activities are regulated by Article 106(2) of Directive 2001/83/EC and Chapter 3 and Article 57 of Regulation (EC) n°726/2004. Pursuant to Article 57 of Regulation (EC) n°726/2004, the EMEA is responsible for coordinating “the supervision, under practical conditions of use, of medicinal products which have been authorised within the Community” (Art 57-c), it must “ensure the dissemination of information on medicinal products authorised in the Community” (Art 57-d), “assist Member States with the rapid communication of information concerning pharmacovigilance to health care professionals” (Art 57-e), “distribute appropriate PhV information to the general public” (Art 57-f) and “co-ordinate the supervision of the quality medicinal products placed on the market by requesting testing of compliance with their authorised specifications” (Art 57-r).

EMEA pharmacovigilance (PhV) activities include:⁹

- ▶ PhV inspections to determine whether the marketing authorisation holder (MAH) has personnel, systems and facilities in place to meet their regulatory obligations under centralised, mutual recognition, and decentralised procedures;
- ▶ Implementation of a sampling and testing programme aimed at supervising the quality of the centrally authorised products available on the European market;
- ▶ Reception of all relevant information, suspected adverse reactions and other PhV data regarding medicinal products for human use which have been authorised by the Community;
- ▶ Collection, storage, management and publication (when relevant) of said information by means of a specific data-processing network (EudraVigilance). This network is meant for the rapid transmission of information to the competent Community authorities in the event of an alert relating to faulty

⁹ Sources: Directive 2001/83/EC; « Procedure for coordinating pharmacovigilance inspections requested by the CHMP », 12 Nov 2007. <http://www.emea.europa.eu/>

manufacture, serious adverse reactions and other PhV data regarding medicinal products authorised by the Community;

- ▶ Where appropriate, issuing of opinions on the measures deemed necessary by the CMHP;
- ▶ Collaboration with the WHO in matters of international PhV;
- ▶ Cooperation with Member States' competent authorities to develop PhV systems that can deliver high standards of public health protection, regardless of routes of authorisation.

The EMEA is not responsible for ensuring that MAHs comply with their obligations regarding PhV. Member States must therefore ensure that all suspected serious adverse reactions occurring in their territory are recorded and reported promptly to the Agency. Member States are also responsible for taking the necessary measures to ensure that a MAH who fails to comply with its obligations is subject to sanctions and/or penalties.

4.2.3. Inspection Services

While the national authorities are responsible for verifying that MAHs comply with the requirements laid down by law in terms of quality and safety of products (manufacture, importation, marketing), the Agency is “responsible for coordinating the verification of compliance with the principles of good manufacturing practice (GMP), good laboratory practice (GLP), and good clinical practice (GCP) and the verification of compliance with PhV obligations” (Art 57 (1) (i)).

On the EMEA Secretariat side, the Inspection Sector (see EMEA organisation chart Figure 1 p.34) is responsible for coordinating inspections, which are realised by inspection teams from NCAs in the EU/EEA. Various inspection team members may be involved in these inspections:

- inspectorates from the country where the Pharmacovigilance officer of the MAH is stationed;
- inspectorates from any EU/EEA country where sites are to be inspected;
- inspectorates from the same country as that of CHMP Rapporteur or Co-rapporteur;
- inspectorates from other EU/EEA country if needed (e.g. for specific expertise).

Those inspectorates, once chosen by the EMEA Inspection Sector, appoint the Inspectors who perform the inspections and reports. There are three types of Inspectors:

- the Reporting Inspector, who is in charge of coordinating the inspection, checking the timelines and writing and co-signing the Inspection Overview (when multi-site inspections are conducted), as well as acting as the main communication point between inspection team and the EMEA Inspection Sector;
- the Lead Inspector(s), who is responsible for the feasibility check, the practical organisation and the conduction of the inspection for at least one site, for the communication between the inspectee party and the Reporting Inspector/EMEA and for the writing and signing of the **Inspection Report**, as well as for the reviewing and co-signing of the Inspection Overview when applicable. The Reporting Inspector may be the Lead Inspector for one or more sites;
- Inspectors belonging to the Inspection Team perform the inspection together with the Lead Inspector.

4.3. EMEA budget

The Management Board is the internal body of the EMEA that is responsible for taking decisions on financial and budgetary matters.

The EMEA has adopted a draft budget for 2009 of 194.39 million Euros. As represented below, EMEA budget has been multiplied by nearly 3.5 since 2000.

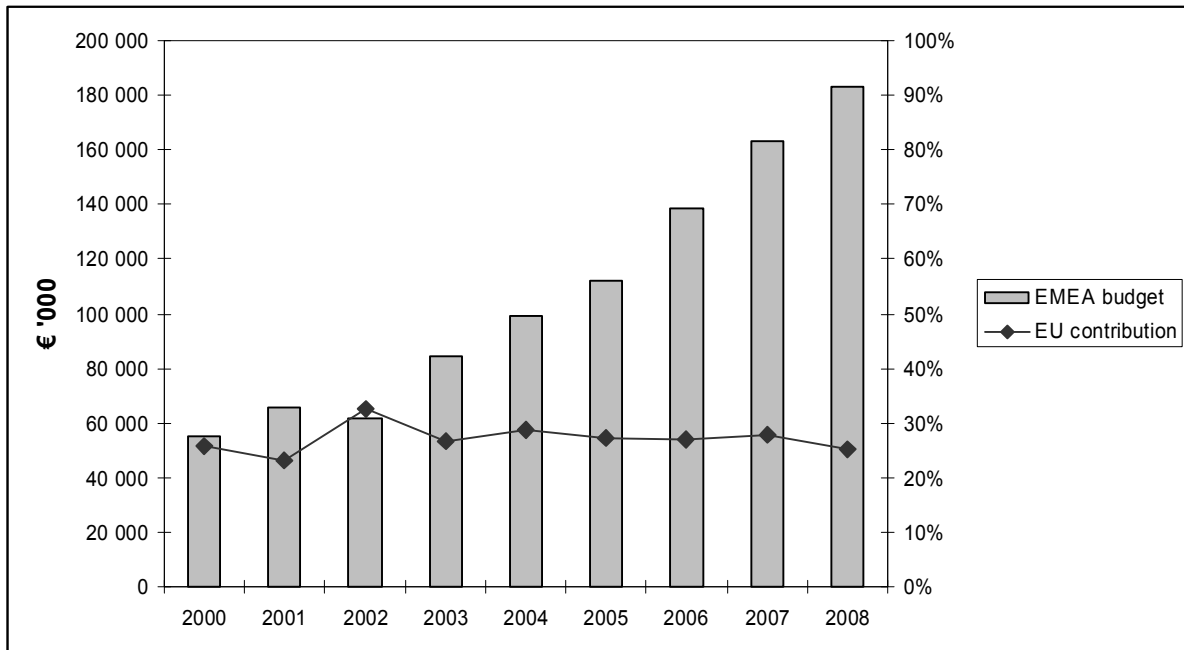


Figure 8: EMEA budget evolution

Source: EMEA annual budgets (2000, 2001, 2002, 2003, 2004, 2005, 2006, 2007, 2008 and 2009)

The following table represents the main revenues:

- ▶ Fees collected: fees payable to the Agency (determined by the explanatory note EMEA/135757/2008 dated November 2008);
- ▶ EC subsidies composed of a general subsidy granted by the European Communities and the contribution from the European Communities to be used exclusively to compensate for fee exemptions for orphan medicinal products (see Figure 8: EMEA budget evolution);
- ▶ Revenues from administrative operations e.g.: bank interest, export certificates, sale of publications, etc;
- ▶ Revenues coming from specific activities undertaken by the EMEA at the request of the EC;
- ▶ Miscellaneous revenue.

And the expenses:

- ▶ Staff expenses e.g.: salaries, allowance, travel expenses, insurance...
- ▶ Buildings, Equipment and miscellaneous operating expenditure;
- ▶ Operating expenses e.g.: meetings, evaluation of medicinal products ((co)rapporteur studies, experts' consultation...
- ▶ Other expenses.

Revenues	2000*	2001*	2002*	2003*	2004*	2005*	2006*	2007*	2008**	2009**
Fees collected	39 236 000	42 708 000	38 372 000	57 943 700	67 350 400	71 895 056	94 556 224	111 752 776	126 318 000	140 966 000
EC subsidies	13 477 033	14 277 522	17 980 683	22 009 700	28 485 264	33 198 060	38 566 159	44 641 992	45 997 000	46 790 000
<i>EC subsidy</i>	12 477 033	13 677 522	15 573 183	19 300 000	24 500 000	27 088 150	31 932 909	39 749 992	39 997 000	40 090 000
<i>Special contribution for orphan medicinal products</i>	1 000 000	600 000	2 407 500	2 709 700	3 985 264	6 109 910	6 633 250	4 892 000	6 000 000	6 700 000
EEA contribution	245 220	287 640	297 920	486 000	536 550	535 940	618 000	798 000	956 000	888 000
Revenues accruing from administrative operations of the institution	1 354 667	2 183 324	1 688 404	2 153 037	2 381 239	3 568 431	5 406 347	6 299 981	5 244 000	4 835 000
Contributions to community program and revenue from services	0	2 312 261	8 500	1 198 153	91 102	0	797 141	582 834	600 000	360 000
Miscellaneous revenue			53 581	572 111	540 870	198 961	1 115 467	1 213 870	3 780 000	550 000
TOTAL REVENUES	54 312 920	61 768 747	58 401 088	84 362 701	99 385 425	109 396 448	141 059 339	165 289 453	182 895 000	194 389 000

Expenses	2000*	2001*	2002*	2003*	2004*	2005*	2006*	2007*	2008**	2009**
Staff	20 413 292	22 974 993	26 216 640	29 680 264	34 150 555	39 307 300	43 708 774	49 871 052	59 245 000	62 186 000
Buildings, Equipment and miscellaneous operating expenditure	11 960 458	12 993 783	10 717 727	19 173 596	23 877 694	26 014 933	34 007 085	44 757 819	50 308 000	51 344 000
Operating expenditure	21 939 170	25 799 971	21 466 721	32 837 626	38 686 159	41 999 799	58 431 224	64 497 206	73 342 000	80 501 000
Other expenditure										358 000
TOTAL EXPENSES	54 312 920	61 768 747	58 401 088	81 691 486	96 714 408	107 322 032	136 147 083	159 126 077	182 895 000	194 389 000

* Outturn year Y as per Final Accounts

** Budget appropriation as of year-end

Figure 9 : EMEA revenues and expenses since 2000

Source: EMEA annual budgets (2000, 2001, 2002, 2003, 2004, 2005, 2006, 2007, 2008 and 2009)

5. Evaluation results

5.1. Effectiveness

*To what extent has the EMEA, as a part of the European medicines network, contributed to an **effective system** for authorisation of human and veterinary medicinal products for the EU?*

Summary:

The EMEA, being defined as the combination of EMEA Secretariat and the contribution of 44 National Competent Authorities, is the key responsible body for the centralised authorisation system. The centralised procedure has shown a growing success over the 2000-2009 period by attracting more and more applicants.

This system together with the whole organisation staying behind is **recognised by all stakeholders** (pharmaceutical companies, healthcare professionals and patient and consumer organisations) as **being very effective**. The following statements, derived from the performed evaluation support the **operational effectiveness of the system**:

- The European authorisation system provides with **complete, clear and highly valued opinions** within regulatory tight deadlines;
- **Best available experts in Europe** contribute to the assessments, contingent on the absence of conflict of interests, so that impartiality of the assessments is ensured. Although the expertise coverage of MS representatives in Committees is not always sufficient, the system encourages the contribution of NCAs internal or external experts, at several stages of application life cycle;
- The **participation of the 30 representatives** to the opinion-making Committees is in line with political prerequisites considering the sensitiveness of these Committees' mandates but also ensures an equal access to information for all Member States;
- **Increased interactions between the stakeholders** (between the representatives of the Member States, but also with the applicants), either formal or informal, have been developed. This increases mutual understandings and therefore contributes to the improvement of the quality of the applications and their assessment reports.

The EMEA Secretariat strongly contributes to the effectiveness of the system. The EMEA Secretariat provides national experts with administrative and regulatory assistance but also increased scientific assistance in specific fields (orphan, paediatric...).

The attractiveness of the centralised procedure together with the EU enlargement and the new regulations have led to an increased workload and an enlarged scope of responsibility for the EMEA over the past ten years. **These changes have led to the creation of new committees (COMP, HMPC, PDCO, CAT)** that required the implementation of additional procedures and new tools. **Those organisational measures contribute to maintain the effectiveness of the system**. The EMEA appears to be a **learning organisation** that shows a permanent willingness to develop an on going improvement process.

However these higher complexity and enlarged scope of responsibility and activities reveal **some weaknesses associated with their specific risks**. The system is progressively attaining its maximum capacity.

- The veterinary system needs its own specific organisation and regulation and no longer being a mirror legislation of the human legislation;
- The main committees are overwhelmed with work and their agendas could hardly be extended;
- The **consistency between the 35 entities** (Committees, WP, SAG...) is a permanent challenge. The consistency is still ensured by specific procedures and management tools, however a risk of overlap exists and has been identified for example between PDCO and CHMP, CAT and CHMP or pharmacovigilance WP and CHMP. They are mainly due to the regulation which is not always very clear on the exact status of the opinions and work issued by these entities. **Guaranteeing the consistency of the opinions remains a permanent challenge for the EMEA**
- As a consequence of the higher complexity, the external stakeholders fear the development of **bureaucracy and rigidity that are challenging the ratio scientific assessment / formalisation in particular for the most complex new entities.**

In this respect,

- the **composition** of the Committees and WP does not systematically fit their **political, scientific and regulatory mandate**. Depending of their scope of responsibilities and main priorities, the “Member State model” may prevail for opinion-making committees as well as certain pre-committees and the “expert model” may prevail for other pre-committees as well as for working parties.
- The **scope of responsibilities** of the Committees is not systematically challenged with regards to their core mandate laid down by the regulation. The management of the increased number of referrals illustrates this trend: they fall systematically under CHMP or CVMP scope when no consensus has been achieved within the deadlines at CMD h/v level.
- Flexibility and pragmatism should be maintained despite higher complexity in the organisation and procedures, notably through regular interactions with external stakeholders.

The EMEA organisation has evolved relatively well considering the recent important changes that the organisation had to face, particularly the 2004 regulation and the EU enlargement. Moreover, the Agency is continuously addressing innovative scientific topics (biomarkers, gene therapy ...) in order to smoothly conduct the changes requested by the permanent research advances. However, the shortage of scientific workforce will certainly be a critical concern in the future. A coordinated effort at EU level may attenuate this deficiency. Finally, the process of “Europeanization” leads to a common organisational logic and convergence of outputs by the EU Member States. The settings of normative activity standards between Member States, and a communal approach to communicate between stakeholders on medicines, are suggestions coherent with this European policy orientation.

The following analyses that allow answering the evaluation question are structured around four main analyses.

- 1. EMEA contribution to the provision of best possible scientific opinion for the centralised authorisation procedure (5.1.1)
- 2. EMEA contribution to the harmonisation of authorisation decisions taken by Member States by resolving disagreement through arbitration procedures (5.1.2)
- 3. EMEA organisation and its contribution to the achievement of the objectives mentioned above (5.1.3)

- 4. EMEA organisation towards recent and future contextual challenges (5.1.4)

5.1.1. EMEA contribution to the provision of best possible scientific opinion for centralised authorisation procedure

The EMEA is delivering an increasing number of opinions for centrally authorised human and veterinary products

The regulation (EC) No 726/2004 resulted in a significant increase of applications for human medicines from 2006 onwards fostered by generic and biosimilar products

The main regulatory reference for the current state of the EMEA authorisation system is Regulation (EC) No 726/2004. This includes corrections of the “operating procedures” and adaptations to take into account the development of science and technology and the enlargement of the European Union, although maintaining the general principles previously established that govern the centralised procedure. It should be noted that, as per Regulation (EC) No 726/2004 and Directive 2004/27/EC, the centralised procedure was made optional for a wider range of innovative products.

Since the modification of legislation and the widening of centralised procedure’s scope, the total number of initial applications for human medicines has doubled (average of 45 in the 2000-2005 period compared to 90 in the 2006-2008 period).

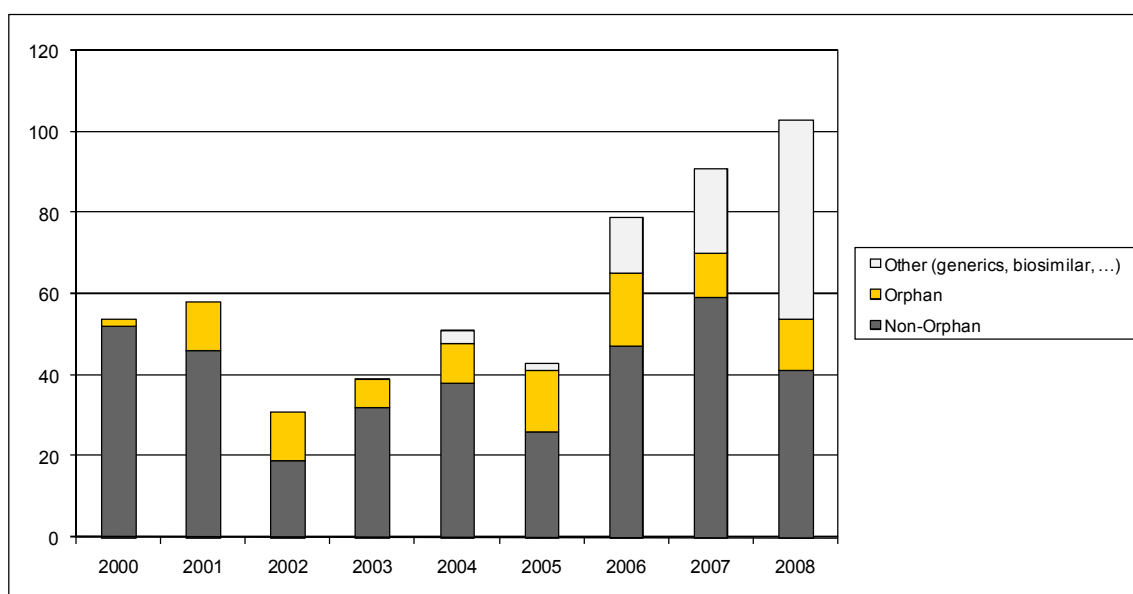


Figure 10: Initial evaluation applications by type of application for human medicinal products going through the centralised procedure

Source: EMEA annual reports (2000, 2001, 2002, 2003, 2004, 2005, 2006, 2007, and 2008)

The rising application for generic and biosimilar products is the main justification for this upward trend for the past three years. Indeed, the generic and biosimilar industry has undoubtedly used this new route of registration for their products (a closer analysis is done in 5.4). This movement will most probably continue as the 10-years data protection period starts to expire for more and more products.

The evolution of the number of applications for veterinary products is consistent with the growing interest of the veterinary industry for companion animals

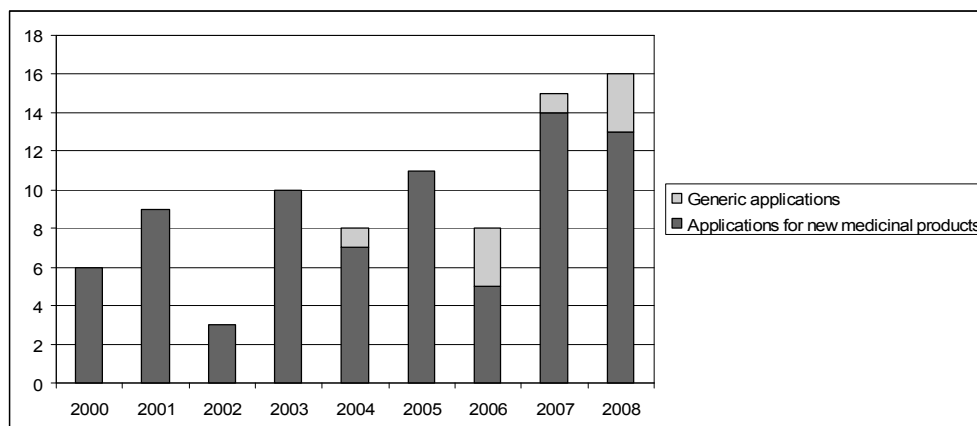


Figure 11: Initial-evaluation applications submitted for veterinary products going through centralised procedures

Source: EMEA annual reports (2000, 2001, 2002, 2003, 2004, 2005, 2006, 2007, and 2008)

Notwithstanding a low number of applications in 2002, there has been a steady increase in the number of new veterinary applications for the centralised procedures. The number of opinions reached has risen simultaneously.

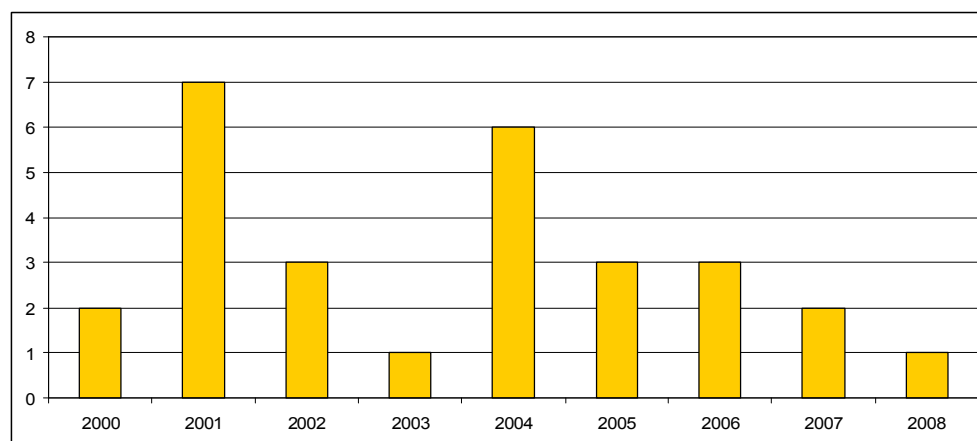


Figure 12: New applications for maximum residue limits

Source: EMEA annual reports (2000, 2001, 2002, 2003, 2004, 2005, 2006, 2007, and 2008)

On the other hand, we detected a continuous decreasing trend in the number of new MRL applications over the past years (see Figure 12). This decline is not going along with an increase of extension applications and extrapolations of MRLs.

The low and decreasing number of MRL is mainly due to the strategy of veterinary pharmaceutical companies. This industry is mainly focusing on the development of medicinal products for pet animals that are not subject to MRL. It has less interest in the food producing animals.

EMA outputs from the centralised procedure are mostly positive opinions

An analysis of the outcome of these applications doesn't lead to a conclusion on whether or not there is a higher proportion of positive opinions over the years. However, there is a high average of positive opinions (about 75% of outcomes for human products are positive on average and about 90% for veterinary products). In some cases, when an "unusual" high number of withdrawals occurs this rate could decrease (for example in 2008, a high proportion of orphan products and applications from SMEs led to more negative outcomes for human products).¹⁰

Some therapeutic groups are more represented in the total amount of applications e.g. immunotherapy and oncology, anti-infectives, medicines intended for the treatment of alimentary tract diseases (see Figure 13 below). This is an indication of pharmaceutical companies' priorities and development fields.

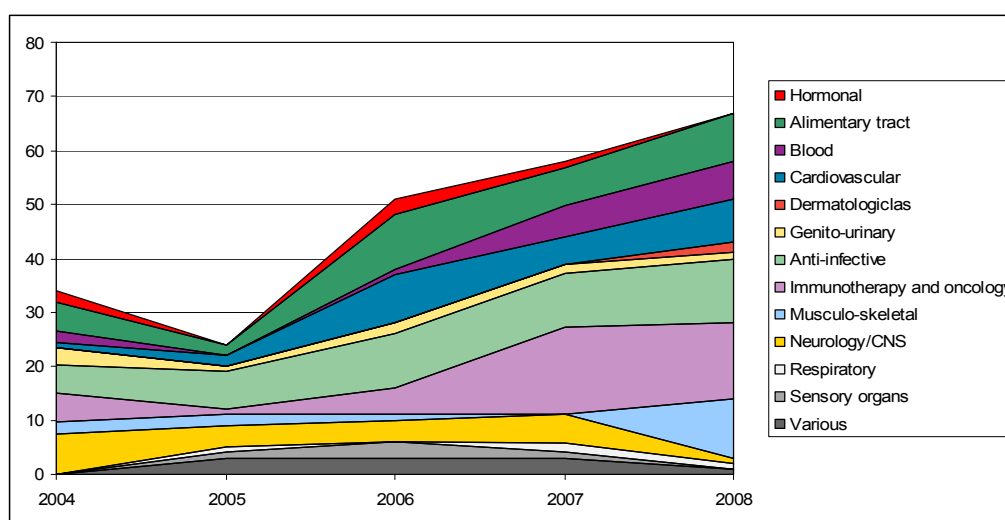


Figure 13: Positive Opinions by therapeutic area for human medicinal products going through the centralised procedure

Source: EMA annual reports (2004, 2005, 2006, 2007, and 2008)

The utilisation of the centralised procedure remained stable compared to other procedures, and is clearly preferred by applicants targeting numerous MS

Besides the centralised authorisation, also national authorisations allow applicants to access specific markets for products which do not fall into the mandatory scope. A national authorisation is issued by the competent authority of an EU Member State for its own territory. This authorisation could be extended to some other countries through the **Mutual Recognition Procedure (MRP)**. This procedure requires an assessment report by the original (Reference) Member State, which is forwarded to the other (Concerned) Member States for deliberation, and finally for agreement.

Compared to the addition of various national procedures which was an option in the past, this formula allows a quicker access to the markets targeted by the applicant. Since it is relatively less costly than the centralised procedure when a small number of countries is considered, the return on investment is

¹⁰ EMA, Survey 2008 on the performance of EMA scientific procedures for medicinal products for human use, March 2009

quicker. This fact makes this procedure particularly attractive for small companies. The veterinary industry which is not interested in launching its product on all National European markets, has also been considering MRP with great interest.

MRP often leads to disagreements between Member States and to additional delays. Consequently, and possibly in order to reduce the potential disputes, a new procedure was introduced by the 2005 new legislation: the decentralised procedure (DCP).

The applicant could apply in several countries at the same time if its product has not been granted any authorisation yet. This is made possible through the **decentralised procedure (DCP)** for which a Reference Member State (RMS) has to be chosen, while engaging all other Concerned Member States (CMS) to which the applicant wishes to apply. From figures 14 and 15, it appears that there is no doubt about the **success of the decentralised procedure**.

DCP is in fact featuring the same advantages as the MRP (quick return on investment). But contrary to the MRP, the applicant doesn't have to wait for the product approval in one country before applying to another one. Not only does it represent a gain of time, but it also reduces the administrative burden for simultaneous authorisation for several countries.

The advantage of the DCP compared to the MRP is further emphasised by the fact that decentralised procedures are less impacted by referrals as of today.

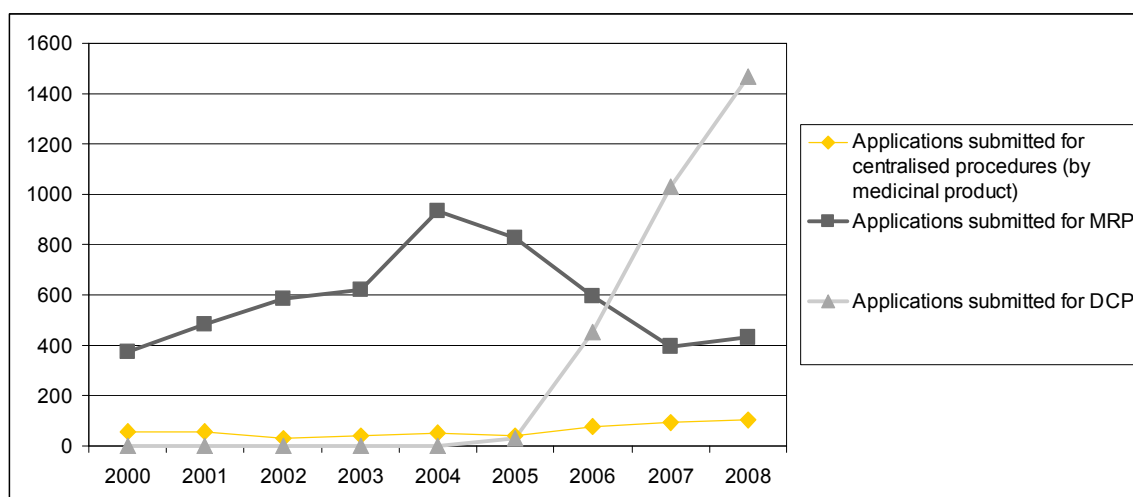


Figure 14: Applications submitted for human products by type of procedure

Source: EMEA annual reports (2000, 2001, 2002, 2003, 2004, 2005, 2006, 2007, and 2008)

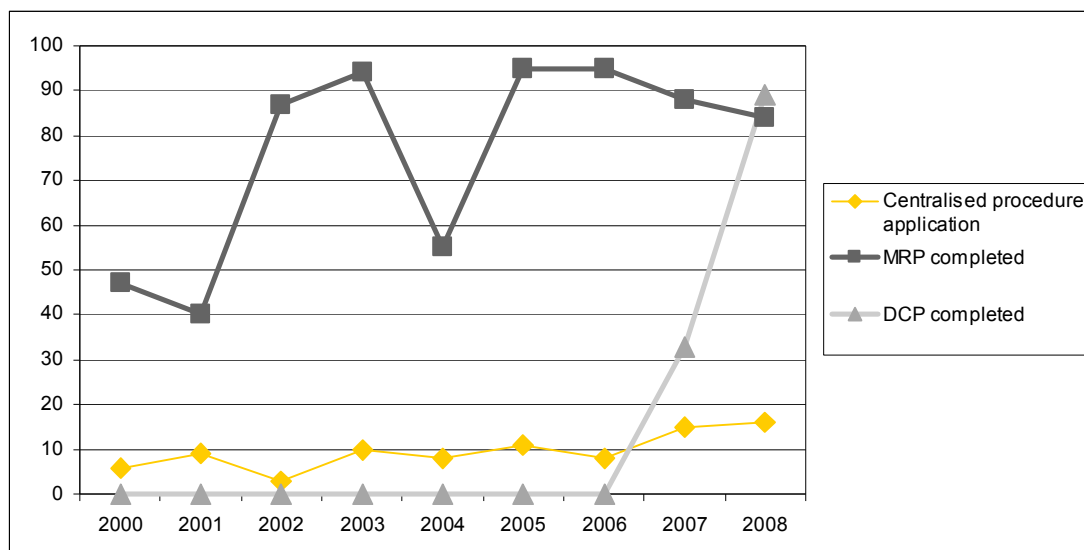


Figure 15: Applications submitted for veterinary products by type of procedure

Source: EMEA annual reports for centralised procedure application figures, IFAH-Europe CMD(v) Survey for MRP and DCP figures

However, even though the DCP theoretically represents an attractive path for the industries in terms of cost and time, the practice has shown some weaknesses. One of the weaknesses is the time necessary to obtain a slot to submit an application for marketing authorisation. The major issue raised is that the majority of DCP are managed by only a very few countries (77% by Denmark, Germany, United Kingdom, and Netherlands) that are suffering from a lack of resources. This imbalance is explained by the willingness of the industries to choose long-term experienced NCAs as reference MS as mentioned during interviews. Efforts to build up the NCA network within the centralised procedure may contribute progressively to enlarge the number of NCAs taking DCP.

This weakness has a particular impact for the generic industry since generics represent the great majority of the applicants, 621 dossiers among the 734 finalised DCP concerned generic products for human use, 74 over 89 for veterinary use). Some companies feel that the centralised procedure is privileged by national agencies, because of the more restrictive European regulatory framework requiring the respect of strict timelines from NCAs.

From an industry point of view, the **centralised procedure** is clearly more attractive than other procedures, when several European markets are targeted. As a matter of fact, new active substances of the optional scope have been increasingly applying for the centralised procedure in 2008 compared to 2007: **optional scope applications represented 56% of 2008 applications whereas the proportion was 37% in 2007.**¹¹ These statistics should however be taken carefully given the weight of generics and the novelty of the DCP, nevertheless the centralised procedure seems to be more and more sought by the industry.

One possible reason for the attractiveness of the centralised procedure relies on its administrative advantages, in comparison with the documents for DCP or MRP required by the different MS and the risks of referrals.

In a long-term perspective, some companies would prefer one single European procedure that allows the flexibility for choosing targeted markets. This is not possible considering the European system due to the subsidiary principle that prescribes maintaining both centralised and national procedures. By some companies, the existence of different procedures may also be considered as an advantage, because they offer various regulatory routes to get marketing authorisation. If some companies are in favour of an

¹¹ EMEA, Survey 2008 on the performance of EMEA scientific procedures for medicinal products for human use, March 2009

extended optional scope for the centralised procedure, other procedures, in particular the decentralised one, are still answering specific needs in terms of marketing strategy.

Considering the current complexity of the European marketing authorisation system in terms of procedures, further development of the regulation may consider the simplification of the regulatory framework toward a smaller number of procedures.

Such evolution should not elude the objective of the centralised procedure to support the increasingly rapid progress of science and therapies in favour of all EU patients (developed in 5.3.1).¹²

Best European experts are involved in the assessment process contingent on the absence of conflict of interests

EMA procedures for handling conflict of interest ensure impartial opinion-making assessment

All scientific experts involved in the assessment processes are made available by the NCAs. EMA procedures are designed to ensure transparency of the appointment process and the absence of conflict of interest for all experts taking part in EMA scientific committees, Working Parties or scientific assessment teams. Such procedures, detailed in EMA Standard Operating Procedures (SOP), apply also to EMA staff responsible for dealing with scientific experts.¹³

Current EMA policies and procedures for handling conflicts of interests ensure that all scientific experts involved in assessments are objective and independent, operating in the benefit of the European public health. The EMA experts' database, which contains data for more than 4500 experts, may however present weaknesses with regards to level in which the information is up to date. Nonetheless, what is most important is the objectivity of the assessors involved in current assessments. Their objectivity is ensured by proper policies and procedures, independently of the database.

Some stakeholders from the industry regret not to have the possibility to choose the MS that will undertake the Rapporteurship for their application, in contrary to FDA procedure where companies can choose their assessors. However, this rule is an additional guarantee for the **independency and objectivity of the assessment**.

The drawback of such strict procedures is that some recognised experts in specific areas where expertise is difficult to find may not be involved in the assessment, because they are working or have been working with the industry. This was pointed out by some NCAs. This occurs especially in Member States where academic institutions and industry are closely linked. This can cause difficulties in areas where expertises are very rare across Europe, such as advanced therapies.

While the independence of the opinion-making committees' members needs has to be strictly ensured, some adjustments to the procedure may be considered for external experts consulted during the assessment as long as a total transparency regarding their links with the industry is clearly established.

Procedures on handling conflicts of interests for such contributing experts may be reviewed in a direction allowing the access to a wider spectrum of experts without jeopardising their impartiality.

A potential improvement could be to weaken some exclusion criteria regarding the date of the last collaboration with the industry. Currently, experts that worked on the topic for a company 5 years ago might be excluded. We suggest looking at these criteria in a more pragmatic way, especially when

¹² Considering 33, Council Regulation (EC) n°726/2004

¹³ EMA Procedure on the Handling of Conflicts of Interest for EMA Scientific Committees Members and Experts (EMA/H/5475/04/Rev1 Final), July 2006

very specific expertise is at stake in situations where NCAs may lack of internal experts and when opinion-making is not involved.

The whole system ensure the contribution of best European experts at several stages of the assessment

Generally, internal stakeholders from the EMEA Secretariat and the NCAs agree that the European authorisation system ensures the contribution of the best available experts in Europe, during several stages of the drug development process:

- In the occasion of the scientific advice, when requested by the company,
- In the assessment teams supporting Rapporteur and Co-Rapporteur;
- Through peer-review process;
- In working parties, scientific advisory groups or ad-hoc groups supporting the work of committees;
- Or in the course of the exchanges before or during the committees' meetings between MS representatives.

At committees level

Rapporteur, Co-Rapporteur and Peer-reviewer are chosen amongst Committees members, the nomination and appointment procedures for MS representatives should ensure the selection of the best European experts.

According to the NCAs, contribution to EMEA activities is very much appreciated by national experts, especially because of the scientific interest (innovative medicines going centrally) and the opportunity to exchange information and knowledge with high qualified European colleagues on similarly encountered problems. NCAs are therefore keen to send their best experts to EMEA's committees, because of this attractiveness of EMEA work.

CHMP and CVMP may not necessary involve all expertises needed for a specific dossier. For instance, the CVMP has lost 4 out of its 7 immunologists and cannot expect to regain that critical expertise soon.

The main reason for this is the nomination process for Committee's representatives. Scientific committee members are nominated by the Member States after consultation of the Management board. However, Member States can nominate an expert irrespective of whether the Board expressed its positive or negative opinion. According to the answers received from to the questionnaire that was sent to the NCAs, Member States consider that the objective of ensuring an exhaustive level of expertise of a greater importance than the criteria of MS representativeness.

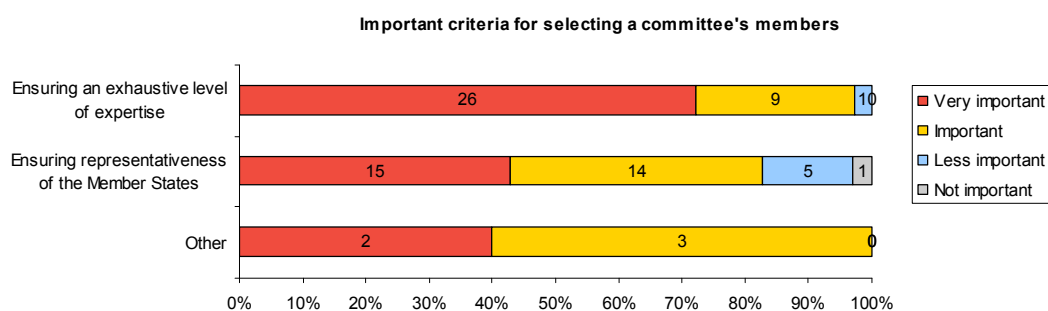


Figure 16: Question 20.1. What are in your opinion, important criteria for selecting a committee's members?

Source: Ernst & Young NCA questionnaire, June 2009

However, the current committee appointment process leads to the appointment of recognised and English-speaking experts from the MS with rather similar scientific backgrounds.

In order to better conciliate representativeness of the committee and scientific competences, the existing procedure should be improved in taking systematically the opinion of the Management Board on each and every proposed appointment.

We suggest having the NCAs propose a few candidates with various profiles and then letting the Management board decide, with the objective of setting up a coherent panel matching all expertise needs.

The current system gives the possibility to involve relevant experts in the committee's opinion-making process: co-opted experts (limited to 5) can compensate the possible lack of key specific expertise in certain scientific committees, for example a statistics expert at CHMP.

Another suggestion for improvement would be to increase the number of co-opted experts. However, the committees are already composed of more than 30 members. The best suitable solution seems therefore to keep the current organisation, but to benefit more from the network in terms of expertises, towards more synergy.

The composition of committees is discussed further in paragraph 5.1.3 as part of the organisational perspective.

Assessment teams level

The assessment is performed by assessment teams under the leadership of a Rapporteur and a Co-Rapporteur, afterwards it is reviewed by Peer reviewers. If the Rapporteur may not have a sufficient level of expertise, and may provide with an incomplete assessment, the Co-Rapporteur and the Peer-reviewers can improve the assessment of the application. All these procedural steps ensure a high quality of the final assessment presented to the committees.

Some NCAs, also invest time in reviewing the applications' assessments, without being involved as Rapporteur, Co-Rapporteur or peer-reviewer. The two reasons for this are:

- To support the motivated opinion of their representative;
- To compensate potential weaknesses of the core assessment teams.

However this is not a very common practice amongst the NCAs, since most of them suffer from a substantial lack of resources (the mobilisation of the network is further discussed in 5.2.2).

The CHMP and CVMP are also relying on inputs from the WP or SAG where national experts in specific fields may contribute to the discussion.

As an interviewee from one of the NCA pointed out, *“EMEA provides high quality work and can draw on a wider pool of experts than any NCA could.”*

The following graph summarizes the results from the questionnaire to NCAs about their assessment of the centralised evaluation system. All respondents are of the opinion that the current centralised evaluation system provides with the best scientific opinion.

This unanimous positive opinion has to be highlighted. More specifically, 84% of the respondents believe that the system is able to provide access to the best available experts in their respective agency. However, less respondents believe that the EMEA authorisation system have access to the best available expertise in Europe, since some experts are on the industry side and therefore excluded to avoid a clear conflict of interests as mentioned earlier.

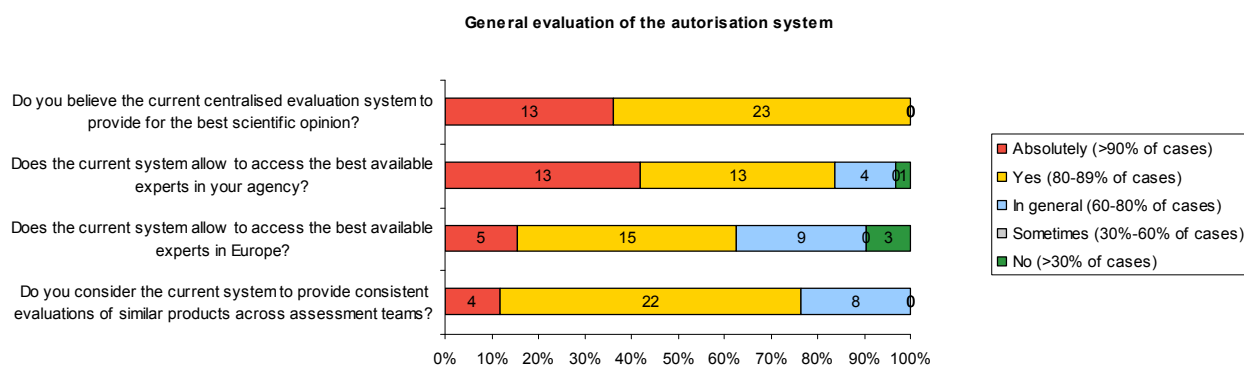


Figure 17: Question 22. General evaluation

Source: Ernst & Young NCA questionnaire, June 2009

According to the legislation and CHMP appointment procedure implemented since September 2006, the designation of Rapporteur and Co-Rapporteur shall be made on the basis of objective criteria, making sure that the use of best available expertise in the EU is used in the relevant scientific area.¹⁴ The CHMP chairman decides on the final Rapporteur/Co-Rapporteur and their assessment team, taking into consideration the following objective criteria:

- Ability of Rapporteur/Co-Rapporteur to fulfil their role;
- Assessment team objective criteria: scientific competence, regulatory experience, sufficient cross-team complementary expertise, and quality assurance skills for the Quality Assurance System (QAS);
- Individual objective criteria: scientific expertise and competence.¹⁵

This procedure should ensure the involvement of the best available experts for human centralised applications. Such an appointment procedure applies for all applications types, with some slight differences. For the CVMP, the appointment process also takes into account the past contribution of the Rapporteur in order to ensure a right balance of Member States' involvement (the mobilisation of the network will be discussed later). This procedure might lead to the appointment of Rapporteurs with more limited experience. However, highly experienced agencies may try to scrutinise all dossiers, in order to ensure consistent quality.

At national agencies level

Finally, the quality of the experts involved in the assessment process depends mostly on the resources of the national agencies and their respective selection procedures. According to the answers to the questionnaire, when gathering an assessment team, NCAs consider expertise in the therapeutic area of interest as the main selection criteria (see Figure 18).

Preference is first given to national experts (internal or external). All stakeholders recognise that international assessment teams would offer a broader expertise. However, administrative and logistic burdens result in highly reluctant NCAs to involve experts from other NCAs (refer to paragraph 5.2.2 for the conditions for the mobilisation of the network).

¹⁴ EMEA, CHMP rules of procedures (EMEA/CHMP/111481/2004), 2004

¹⁵ EMEA, CHMP Rapporteur/Co-Rapporteur appointment: principles, objective criteria and methodology, 12 July 2006

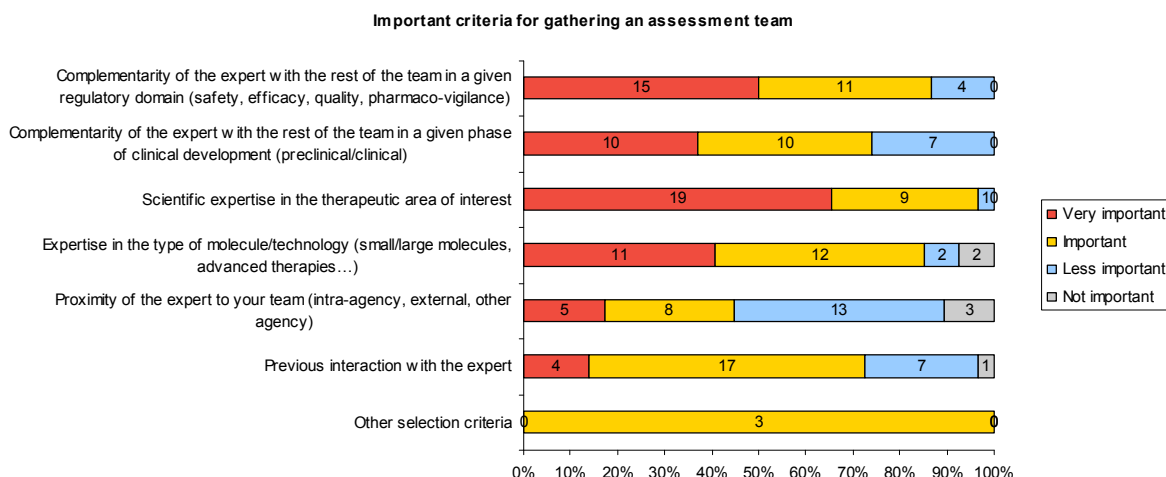


Figure 18: Question 13. Please rate the importance of the following selection criteria when gathering an assessment team (team of assessors/experts assisting the Rapporteur and Co-Rapporteur)

Source: Ernst & Young NCA questionnaire, June 2009

In terms of available expertises across Europe, the results show that some specific technologies are less represented than others. For instance, less than one third of the respondents claimed to have some expertise in-house on gene or cell therapies or tissue engineering.

As on figure 19, contracting out is often a solution for NCAs lacking expertise or sufficient resources. Clinical and research expertises are the most frequent subcontracted areas of expertise.

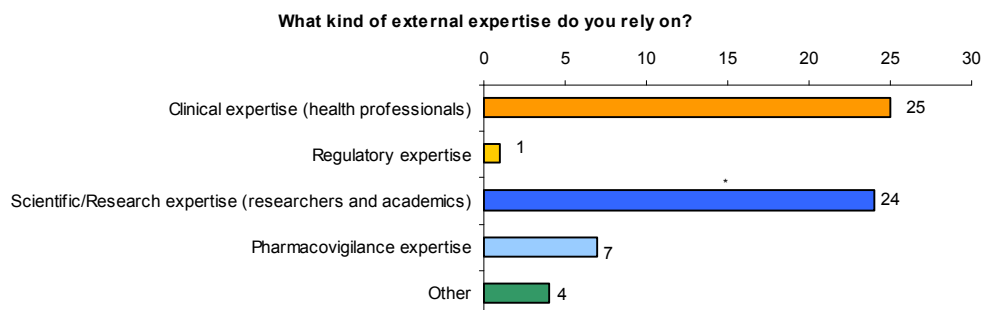


Figure 19: Question 14.2. What kind of external expertise do you rely on?

Source: Ernst & Young questionnaire, June 2009

In terms of regulatory expertise, small agencies pointed out a lack of expertise for the Environmental risk assessment (ERA), especially on the veterinary side.

Portugal / Hungary: external experts to compensate constrained internal resources

- ▶ The Portuguese agencies (Infarmed for the human side and DGV for the veterinary side) face an important lack of resources coupled with an increasing workload. They have therefore decided to open their expert database to all experts keen on contributing to the NCAs work:
 - For a few years, the DGV had 8 internal experts to perform all assessments required by different types of procedures. Currently, DGV internal experts are more involved in the making sure the dossiers are drafted in accordance with EMEA guidelines while the assessment are mainly performed by external experts;
 - Infarmed is also often contracting out its assessment work, relying mostly on clinical and research expertise;
 - Some external experts that are contracted by DGV are taking part in some Working Parties (scientific)
- ▶ The Hungarian Human Agency (OGYI) usually works with 40 external experts since the number of internal staff members has reached a saturation point.

Key learnings:

- ▶ Outsourcing assessment work can be considered as a convenient short-term solution for agencies facing a lack of scientific human resources. The use of outsourced resources may offer more flexibility than the recruitment of new internal experts, in order to answer quickly to the applications;
- ▶ An important limit when contracting out the assessment work is the availability of relevant expertise in a MS, taking into consideration to the absence of a conflict of interests. In Hungary, experts from universities or research institutes are often involved in industrial research. Links between academic and the pharmaceutical industry are particularly strong in this country;
- ▶ In the long term, relying mainly on external expertise presents also some risks and does not seem to be sustainable:
 - External experts taking part in EMEA WP are less keen to share their knowledge;
 - An important amount of work is performed after the authorisation. If the assessment relies only on external expertise, this might become an issue for post-authorisation work (for example for variations or PSURs, in the case that the involved external expert is no longer available. It is important for the NCA to keep the assessment knowledge in-house;
 - EMEA's responsibility is to ensure that knowledge management and transfers to NCAs experts are ensured.
- ▶ The recruitment of new scientific staff by NCAs may be constrained by national regulations for hiring civil servants that are very often very strict and provide less flexibility to adapt to an increasing workload.

Even if the lack of resources depends mainly on national recruitment policies, the EMEA Secretariat could facilitate the identification of relevant experts for NCAs facing such problems. The EMEA has already built up an expert database, but NCAs are asking for further support.

A possible solution could be to strengthen the interactions between human and veterinary agencies. In some MS, the only contact between both agencies takes place within their national office in the EMEA building. As some expertises are common to both types of assessment, human and veterinary,

expertises should be shared, such as NCAs with mandates at the national level.

Applicants show a great satisfaction regarding the EMEA centralised procedure, but also increasing expectations

Companies are globally highly satisfied with the centralised procedure and interactions with the EMEA Secretariat

Overall companies are highly satisfied with the centralised procedure and their interactions with the EMEA. In comparison with the DCP and MRP, the centralised authorisation system is far easier from an administrative point of view and provides also with high-valued scientific opinions. A company synthesises the perception of what have been achieved since the creation of the Agency: *“Over the past 15 years, EMEA has done a good job in building a reputation of a world class science-based regulatory Agency which enjoys the trust and confidence of its many stakeholders”*.

The level of the fees is generally considered as high, but acceptable compared to fees associated with DCP or MRP (refer to 5.4.1 for further discussion of this topic). This high level of fees has also been impacting the industry expectations.

The main strengths and weaknesses mentioned by industry stakeholders are listed below:

Strengths	Weaknesses
<ul style="list-style-type: none"> ▶ Quality of the scientific assessment, perception of high scientific requirements; ▶ Constructive dialogue between applicants and assessors; ▶ Reliability: <ul style="list-style-type: none"> – Fixed timelines; – Transparency; – No risk of referrals; ▶ Accessibility of the EMEA Secretariat, also through informal ways; ▶ Less administrative and bureaucratic than DCP (national issues) or MRP: a unique file for initial evaluation and for variations. 	<ul style="list-style-type: none"> ▶ Heavy requirements (notably for small companies) in the final phase: <ul style="list-style-type: none"> – Translation of packaging is perceived as a burden (23 languages); – The QRD (Quality Review of Documents) which looks at the product literature (label, box, packet insert) focuses sometimes too much on formal details that are not dealing with scientific issues; – Little flexibility in the mock-up validation process; – The request to include local distributors in the leaflet even for those countries where the product will not be marketed; ▶ Some inexperienced EMEA project managers may lack flexibility; ▶ Some difficulties to arrange meetings with Rapporteur and Co-Rapporteur; ▶ Insufficient level of contact between the Rapporteur and the Co-rapporteur.

Human pharmaceutical industry representative organisations have identified some potential areas of improvement in the assessment process

The industry organisation EFPIA (European Federation of Pharmaceutical Industries and Associations) provides regularly evidence based feedback on EMEA procedures to EMEA. The results of the 2006-2008 surveys were presented during the EMEA-EFPIA Info Day on February 24th, 2009:

- ▶ EFPIA expressed their satisfaction regarding the pre-authorisation procedures, except for orphan drugs for which they had more comments;
- ▶ Companies show a high level of satisfaction with the quality, clarity and completeness of assessment reports. However, satisfaction scores are lower in the last 2006-2008 survey than in the 2005-2006, particularly the clinical aspects of the assessments. Some inconsistencies in the assessment of product information are also reported;¹⁶
- ▶ Applicants are still satisfied with the procedure timetable, the EMEA organisation, especially the product team leader, and the communication between EMEA and the industry. Nevertheless, satisfaction regarding the oral explanation is decreasing, notably with regards to interactivity and scientific adequacy of the discussions;
- ▶ Satisfaction of companies regarding EMEA procedures for the extension of applications is clearly higher than for new applications. Good communication and flexible attitude are well appreciated. Possible improvements would be the substantiation of comments;
- ▶ Scientific Advisory Groups (SAGs) are considered as well-organised and supportive experts groups, however showing room for improvement:
 - Companies are asking for more transparency of SAGs work towards the applicant;
 - Waivers to conflict of interests considerations should be considered to ensure the involvement of key experts on specific topics;
 - The same quality of meeting conduct should be ensured from one SAG to the other.

Like other pharmaceutical industry representative organisations, EFPIA is strongly satisfied with the quality of interactions with the EMEA and wishes to continue in this way. This collaboration deals notably with the following key topics that will be discussed later:

- Electronic submission (see 5.2.1);
- Paediatric regulation (see 5.3.2);
- EMEA product naming policy (see 5.4.1).

Vis-à-vis EMEA Secretariat, EFPIA supports EMEA's ambition to implement measures to enhance continuous dialogue around the Product Team Leader (PTL), with some concrete propositions:

- ▶ The PTL should act as an “account manager” towards the applicant,
- ▶ As soon as the Rapporteur is selected for an application (for Scientific advice or later), he/she should remain the leading person during the whole product lifecycle, in order to ensure consistency of the opinions.

¹⁶ This perception should be balanced by the fact that a higher percentage of procedures ended in rejection or withdrawal over the 2006-2008 period.

The veterinary industry representative organisations points out the lack of specialisation of the regulation to the veterinary field as well as some bottlenecks

On the veterinary side, the IFAH (International federation for Animal Health) provides balanced feedbacks, identifying also the specificity of the veterinary sector:¹⁷

- ▶ Veterinary companies point out the effective running of the procedural aspects of the centralised authorisation system:
 - Pre-submission meeting is seen as very useful by applicants, the participation of the Rapporteur bringing great value for discussions on technical aspects;
 - The oral explanation is considered as a good opportunity to get into direct contact with the CVMP and resolve pending issues;
 - The decision making process (DMP) works well for the majority of applicants.
- ▶ Some bottlenecks were also identified by veterinary companies:
 - The interpretation of guidelines may lack flexibility in some areas, notably user safety, environmental risk assessment, quality and compliance with monographs;
 - Companies face important difficulties for the finalisation of the SPC wording and translations.
- ▶ IFAH expresses also a general complain about the lack of adaptation of the regulation to the Veterinary sector.¹⁸ This is taken into account with the on-going impact assessment of the veterinary pharmaceutical legislation lead by the European Commission.

Synthesising applicants feedbacks, some recommendations regarding the steps of the centralised procedure have been outlined:

- ▶ The preliminary meeting is considered as very useful for applicants. That is why companies would like to have this meeting earlier in the process and also to involve systematically the Rapporteur;
- ▶ During the whole assessment process, applicants would like to see a certain continuity at two levels:
 - at the EMEA Secretariat level through a single contact point as for example the Product Team Leader (PTL);
 - at the scientific assessors level and in particular between Scientific Advice coordinator and Rapporteur/Co-Rapporteur for the initial assessment (there is currently no formal link between these experts);
- ▶ Considering the difficulties related with the final phase, companies pointed out some room for improvement towards a smoother process:

¹⁷ IFAH, Centralised Procedure survey (2005-07) – Follow-up to the benchmarking survey (2006), December 2008

¹⁸ IFAH, Promoting a positive environment for veterinary medicines, February 2008

- the possibility to discuss SPC wording before day 180;
- an increased cooperation between QRD and CHMP/CVMP;
- more flexibility regarding translation requirements.

In a nutshell, companies express mainly minor complaints, but are concerned about a possible evolution of the EMEA towards a more bureaucratic organisation, lacking flexibility.

Both human and veterinary industry organisations acknowledge the **continuous improvement of interactions between the EMEA and the industry**. Relationships between EMEA and the industry are now based on mutual trust, with three types of interactions:

- very informal interactions;
- formal contacts: through bilateral meetings or Infodays;
- consultation procedures for documents, leading to the production of a position paper.

Industry organisations wish strongly to continue to build up on this collaboration.

The high quality of EMEA scientific opinions is also recognised by NCAs

NCAs recognise the output quality of EMEA scientific procedures

According to the Ernst & Young survey, a large majority of NCAs consider the output of the centralised procedure to be of good quality. **All types of EMEA procedures seem to achieve a high level of quality for the NCAs**, as represented in the following graph, **but the centralised procedure is the one that is most highly valued**.

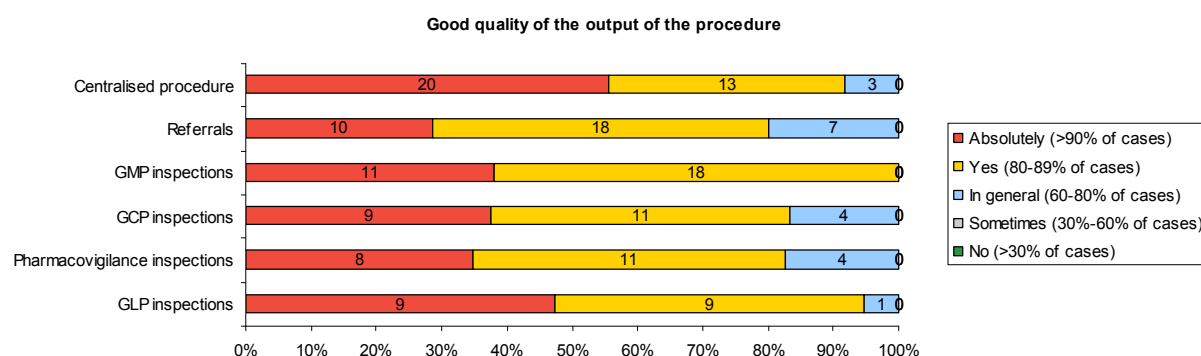


Figure 20: Questions 16.1 / 17.1 / 19.1 / 19.3 / 19.5 / 19.7: Do you consider the [procedure] to be of good quality,

Source: Ernst & Young NCA questionnaire, June 2009

Most NCAs are satisfied with the centralised procedure as it is currently regulated: 87% of respondents do not wish a shortening of the timelines, 53% are not in favour of an extension of the centralised procedure to other products (28% in favour and 19% expressing no opinion), and less than one third think that some aspects could be simplified.

In terms of scientific quality, interviewed experts from NCAs mainly rate EMEA opinions from good to outstanding. A CHMP member summarises this view: “You can argue that the assessment process is

sometimes flawed, that the quality of Rapporteurs' reports is not always good or that timelines are not respected (internally), but at the end of the day the quality of the outcome is very good."

However, some concerns and weaknesses are pointed out requiring regular review of the procedures and sometimes more flexibility

The quality of the assessment may vary, depending on the NCAs and experts involved in the assessment team. The lack of resources may impact the completeness of the assessment (the mobilisation of the network is further discussed in 5.2)

Some assessors complain about bureaucracy and rigidity that are increasing, and may impact the quality of the assessment dossier: *"Sometimes applications would need more time to be completed than with planned timelines. With more time, you could have different assessments. There is no adaptation of the system to the complexity of the molecule."* More time or the opportunity to go back to the company may be sometimes be useful for the assessors, in case of more complicated applications.

As already suggested by applicants, some flexibility and pragmatism with timelines and in particular regarding final discussions with the applicant could sometimes help to provide with a more solid and balanced assessment. For veterinary products, safety issues like antibiotic resistance, residue limits or environmental risk should be similarly more carefully considered.

CHMP members regret also the **lack of time to send comments** (only 10 days between day 150 report and day 160 sending in recent EMEA timetable). Recent Acomplia and Raptiva cases revealed some difficulties in the review process, notably considering limited feedbacks from CHMP members. The timing issue should then be considered as a possible constraint in the review process.

On a broader view, assessments' timetables should be regularly reviewed, with the objective to better balance the timelines in favour of the scientific assessment. For instance, the Product Team Leader could tend to focus only on deadlines, without putting them into the perspective of public health and scientific issues raised.

Another potential difficulty is the consistency between the different EMEA opinions. The Secretariat has to ensure that assessments for similar products cannot be contradictory (see the paragraph about the allocation of tasks between the different committees and possible contradictions, in 5.1.3).

In order to ensure the quality of its authorisation procedures, the Swedish agency (MPA) has put in place a structured Quality assurance process ensuring consistency between the dossiers. It has been identified as a good practice for other agencies and the EMEA.

As stated in the EMEA Road Map to 2010, the implementation of "a robust quality assurance system helps to guarantee the overall quality and efficiency of its operations." The EMEA is already making substantial efforts in this sense, analysing regularly rooms for improvement, and should go further through improving the structure of this process.

The only nuance in terms of scientific quality of EMEA outputs refers to the assessment of variations that may be of less good quality than initial assessment, as assessors tend to stick to their old assessment.

Veterinary procedures face specific problems raised by NCAs

The scientific quality of EMEA opinions on veterinary products is also considered as largely satisfactory. However, some specific difficulties and risks are pointed out.

NCAs confirmed that the CVMP and some NCAs are **lacking veterinary immunological experts**. The CVMP is using statistical method to assign the Rapporteurship and the resulting appointed NCA may lack of such expertise. NCAs consider that the system shows some pragmatism and compensate

through the inputs of qualified experts from other NCAs, so that the quality of the assessment is not impacted.

Some NCAs pointed out the risk for the CVMP to derive towards a simple registration office, considering that it is easier for a CVMP Member to give a positive opinion than a negative one. The CVMP is still giving negative opinions and some applications are also withdrawn before the end of the assessment. However, the question raised deals with the opinion-making process at the CVMP: does it currently ensure fair and transparent opinions and in particular with respect to efficacy matters? Considering the objective of the CVMP to express positive opinions for products, whose quality, safety and efficacy have to be proved with regards to the risk-benefit assessment, veterinary experts recognise that there is no authorised product with remaining safety issue, however they may express more doubts on the efficacy part. This point has also to be considered with regards to the specificity of veterinary medicines that are often targeting unmet needs.

In order to ensure a broader recognition of CVMP opinions among European veterinary experts, the opinion-making process at the CVMP may be reviewed towards greater transparency. Diverging opinions are currently put in the appendix of the CVMP opinion, but are not published.

It could also be relevant to justify in written a positive opinion, when differing opinions have been expressed.

5.1.2. EMEA contribution to the harmonisation of authorisation decisions through arbitration procedures

EMEA arbitration procedures and Community referrals show a great increase that impacts the effectiveness of the whole system

The EMEA is dealing with two main types of referrals, initiated by companies, Member States or the European commission, that are impacting its activities:

- ▶ On the one hand, arbitration procedures initiated following a disagreements between MS or a disagreement between the marketing-authorisation holder and some MS in the framework of the MRP or DCP:
 - for human medicines: either under Article 29 of Directive 2001/83/EC as amended or Articles 6(12) and 6(13) of Commission Regulation (EC) No 1084/2003;
 - for veterinary medicines: under article 33 of Directive 2001/82/EC as amended.

Since 2005, these referrals have been managed by the CMD(h) or CMD(v), which are under the responsibility of the Heads of Medicines Agencies (HMA). Their secretariat is managed by the EMEA. The Member States represented at the CMDh/v shall make their best to reach an agreement within the 60 days deadline after the disagreement is expressed. If no consensus is reached, the matter is transmitted to the CHMP or CVMP according to the nature of the product.

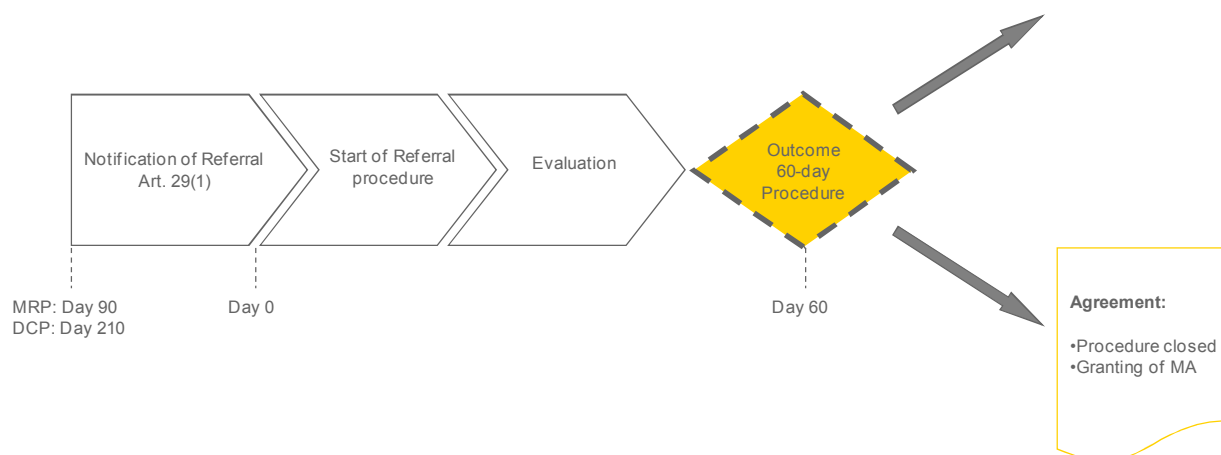


Figure 21: Flowchart of the CMD 60-day Procedure

Source: CMDh, Presentation for 5th TOPRA Annual Symposium in Budapest

- ▶ On the other hand, Community referrals are going directly to central committees (CHMP/CVMP) to obtain an opinion based on a scientific assessment. These procedures are based on the following grounds:
 - Article 31 and 36 (Articles 35 and 40 for veterinary medicines) referral procedures are mainly initiated in case of Community interest and generally for safety-related issues;
 - Article 30 referrals (article 34 of Directive 2001/82/EC for veterinary medicines) are mainly initiated in order to obtain harmonisation of authorisations for medicinal products authorised in the Community by Member States;

- Article 107 procedures under Directive 2001/83/EC, as amended, are initiated to obtain a CHMP/CVMP opinion further to the suspension or revocation of the marketing authorisation of a medicinal product in a Member State as a result of pharmacovigilance data;
- Article 5(3) procedures under Regulation (EC) No 726/2004 require a CHMP/CVMP opinion on any scientific matter raised by the EMEA, the European Commission or a Member State.

The adoption of the CHMP/CVMP opinion on referral procedure shall occur within 60 days following the notification of the referral (considering clock stop when the Applicants/Marketing Applicant Holders has to prepare the responses to CHMP).

Referrals for human medicines have doubled since 2001, in particular arbitration procedures and Article 30 referrals

Figure 22 shows the evolution of referrals for human medicines and their origin since 2001. This graph reveals the strong increase of referral procedures in the last few years, which has a clear impact on EMEA dedicated resources. The greatest increase concerns arbitration procedures that are still representing almost 50% of referrals dealt with. Between 2003 and 2005, this proportion was near to three quarters of the total amount of procedures referred to CHMP, even though this share has clearly decreased since the creation of the CMDh in November 2005.

Article 30 referrals are now representing around one third of referrals.

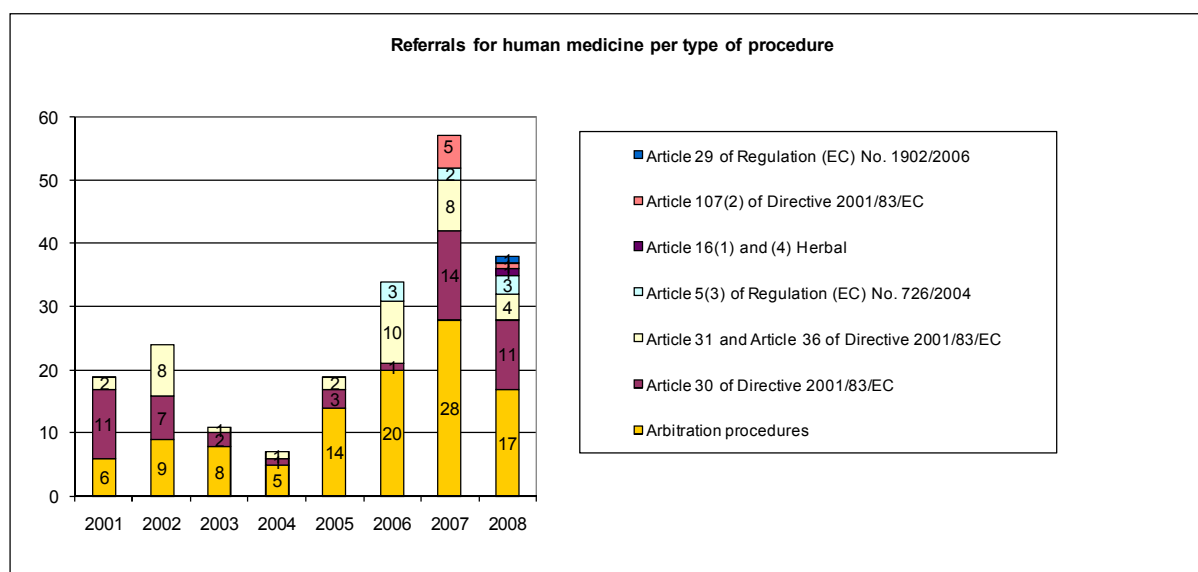


Figure 22: Evolution of referrals for human medicine per type of procedure since 2001

Source: EMEA annual reports (2000, 2001, 2002, 2003, 2004, 2005, 2006, 2007, and 2008)

MRPs generate more often referrals than decentralised procedure (see Figure 23). In 2007 and 2008, the number of MRP referrals transmitted to CHMP represented almost half of the referrals.

However, since DCP generates less referrals than MRP, the evolution of arbitration procedures is expected to follow the decrease of the MRP.

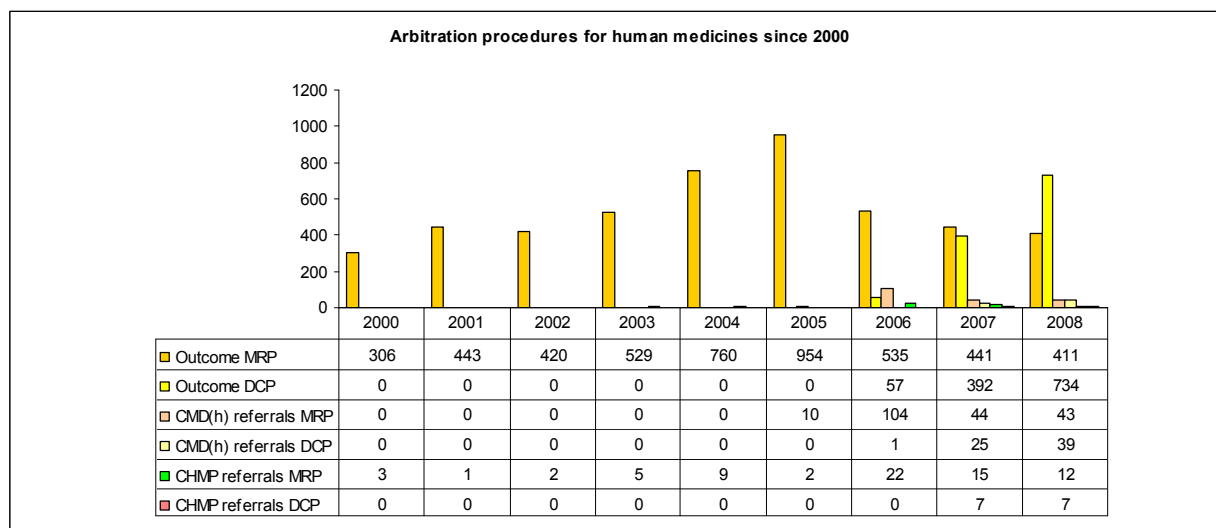


Figure 23: Evolution of arbitration procedures for human medicines since 2000

Source: CMD(h) statistics

Even if the CMDh is handling most referrals, a lot are still transferred to CHMP, not only for scientific issues, but also because a consensus has not been reached within the 60-days deadline, even on a non scientific matter.

Referrals and arbitrations for veterinary medicines have tremendously increased but the impact on the organisation is far more important mainly because of the generated workload for referrals

Since 2002, the number of referrals for veterinary medicines has more than doubled. The major part of this growth concerns arbitration procedures (see Figure 24), but interviewed experts underlines that article 34 and article 35 procedures are far more time and resource consuming.

More generally, experts pointed out the growing complexity of referrals covering a very wide range of products, each of them requiring specific attention. The number of referrals is thus not representative of the workload.

The CVMP has currently to cope with finding volunteer who would accept a referral dossier (non-compensated) that comprises sometimes 100 to 150 products and organising the CVMP agenda according to the referrals requirements.

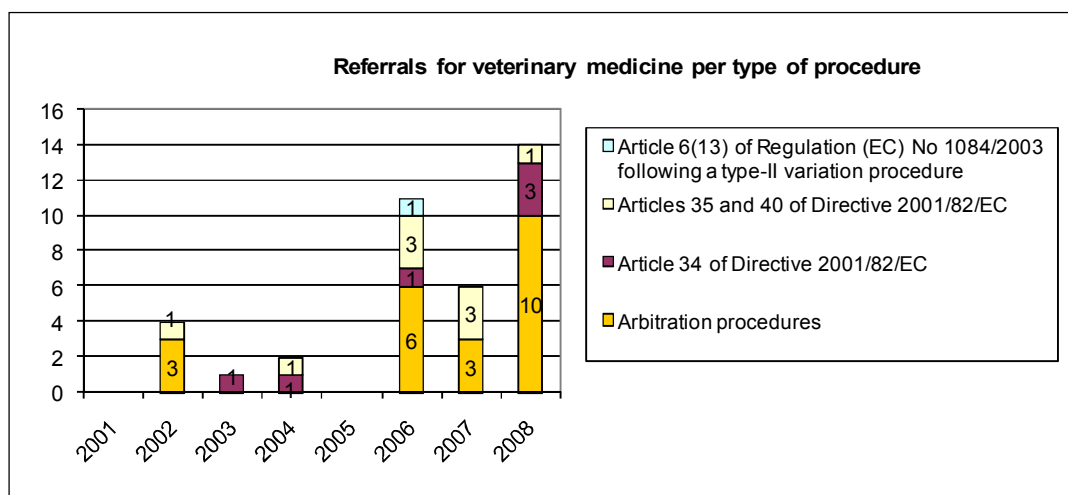


Figure 24: Evolution of referrals for veterinary medicine per type of procedure since 2001

Source: EMEA annual reports (2000, 2001, 2002, 2003, 2004, 2005, 2006, 2007, and 2008)

Considering more precisely arbitration procedures (see Figure 25), around 10% of MRP and DCP for veterinary medicines are generating referrals.

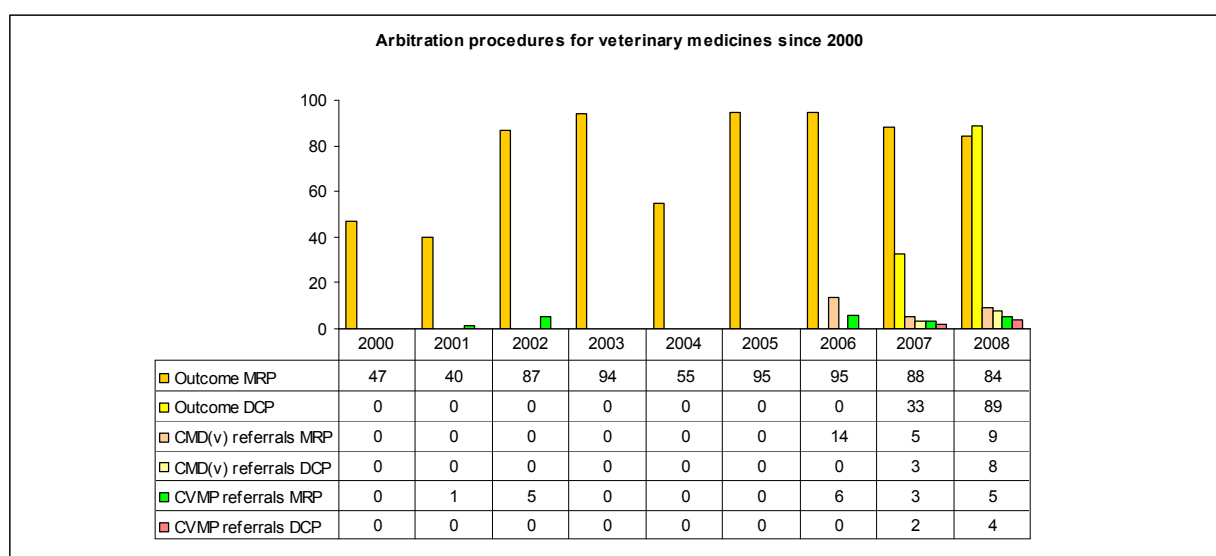


Figure 25: Evolution of arbitration procedures since 2000

Source: CMD(v) statistics

Contrary to human medicines, MRP do not follow a downward trend: the number of MRP remains quite stable, while the number of DCP is increasing. In terms of arbitration procedures, the total number of MRP and DCP referrals is still quite low, but there are generating an increasingly important workload (especially Art. 34 and 35 referrals) requiring an adapted organisation.

The increase in the number of arbitrations and referrals is mainly linked with the harmonisation process of MRP and DCP

Human and veterinary referrals come mainly from different interpretations of the directive 2001/83/EC and 2001/82/EC for vet products, leading to a transition period of organisational adjustment

Currently, main grounds for referrals are reported as dealing with:

- Withdrawal periods,
- Label licensing,
- SPC harmonisation.

Member States may still have different interpretations of the regulation and guidelines, but differences should progressively be alleviated.

The learning process should also concern the industry side, for which referrals cause important additional costs and delays before the marketing authorisation.

Some experts and EMEA staff members consider that referrals are a legacy of the European history that should decrease within the following years. This transition phase may need some organisational adjustments, but should not impact EMEA activities over the long-term. Some NCAs experts perceive already a decrease of referrals going to CHMP/CVMP.

Member States are already trying to address those issues in the framework of the CMDh/v. Eastern European countries have for instance created a labelling and packaging subgroup on a voluntary basis. This group aims at facilitating the authorisation of common labelling for different Eastern European countries.

Such topics may need further guidelines to improve harmonisation of industry dossiers on the one hand, and NCAs assessment on the other hand.

The contribution of the European Commission is also of great importance, notably for the interpretation of the directive 2001/83/EC regulating MRP and DCP.

The veterinary sector faces additional regulatory issues with the European Reference Product referrals developed in section 5.4.4

In terms of legal basis, the European Reference Product represents another important cause for referrals for veterinary medicines. An authorised product in a Member State may be genericised in another MS without any specific assessment before marketing authorisation. This causes problem especially for old authorised products, for which MS may not be able to provide with sufficient data. Experts from NCAs point out the negative impact of the weak implementation of the legal framework by the MS not only on referrals and the related workload, but also on the distribution of medicinal products without a satisfying assessment.

Despite global satisfaction regarding referrals and arbitration outputs, organisational changes may be necessary to sustainably absorb the increased workload

In terms of quality, 28 out of 35 responding NCAs on this topic consider the output of referrals to be of good quality in more than 80% of cases.

Applicants also seem to be globally satisfied with the referrals procedure, article 31 referrals (generally for safety-related issues) being reported as more specifically efficiently monitored. According to an industry organisation, article 107 will certainly be the most used procedure in the future.

Yet, room for improvement has been identified by industry interviewees:

- In terms of transparency of the process;
- In terms of respect of referrals' output;
- The EMEA may improve the transparency of arbitration and referrals procedures, but the control of referrals decision implementation in Member States depends on the European Commission. Some applicants even regret the lack of an appropriate appeal procedure after referrals decision as a usual adjudication.

On the referrals timelines subject, there is not any consensus between companies, in favour of referrals timelines reduction, and NCAs, 69% of respondents to the questionnaire being indeed against the shortening of these referrals timelines.

However, both types of stakeholders agreed on the potential benefit of an organisational change in referral procedures. The transfer of a dossier between CMDh/v and CHMP/CVMP is considered by companies as an important bottleneck. Referrals dealing with scientific issues should be sent directly to CHMP/CVMP. On the contrary, NCAs experts consider that referrals transferred to CHMP/CVMP and dealing with the interpretation of the regulation should have been addressed through an agreement between MS.

The increasing workload implied by referrals is clearly identified as unsustainable by experts with regards to resources needed for EMEA core activities. This situation requires an adaptation of the current organisation to face the workload without jeopardising EMEA core activities.

Some courses of action have been identified, during the different interviews, that may be combined and articulated in different ways:

- ▶ The CMDh/v could be strengthened by HMA, in order to improve its capacities to reach an agreement, before transferring a referral dossier to the CHMP/CVMP, in particular when the subject is not dealing with scientific issues;
- ▶ The workload of CHMP and CVMP could be lightened through the creation of a sub-committee with one representative per MS dedicated to referrals. This could be an interesting solution, as some experts consider referrals as a good activity for NCAs to gain experience for dossier's assessment. The role of referrals in this extent should not be underestimated;
- ▶ NCAs experts pointed out as an important difficulty the fact that a lot of referrals, not initiated by companies, do not imply any funding for NCAs. CVMP finds it more and more difficult to find volunteers for referral Rapporteurship, as it is an important burden for Member States, without any counterpart. This financial issue will be further discussed in 5.2 along with other non-fee related activities. Regarding referrals, the funding of referrals dossier transferred to CHMP/CVMP may be considered, as it deals theoretically with scientific issues.

5.1.3. Contribution of EMEA organisation to its objectives of terms of effectiveness

Although the meaning of an effective organisation could be discussed, its design and its coordination shall observe certain principles in order to effectively contribute to the organisation objectives accomplishment.

Before considering the internal organisation of the EMEA Secretariat, the Agency shall ensure that its activities are well understood by stakeholders, i.e. all the groups that influence or are influenced by the EMEA actions. Considering the scope of activities of the EMEA, the following groups are considered as stakeholders: pharmaceutical industries (and particularly its research and development departments), regulators within the European Union, national governments and healthcare institutions, healthcare professionals, patients and European citizens.

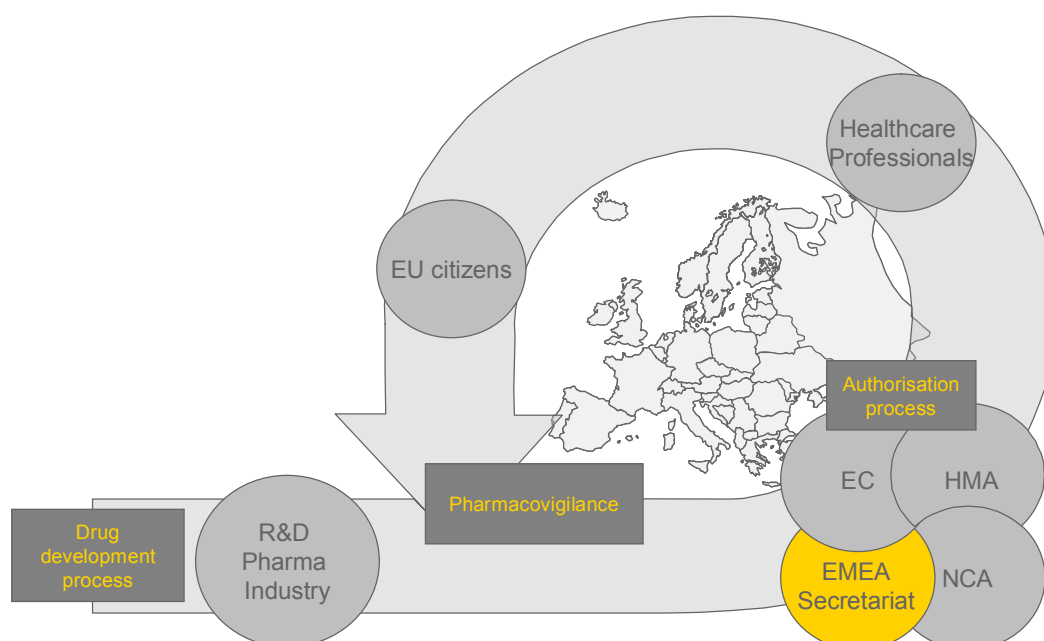


Figure 26: Stakeholders of the European authorisation system for medicinal products

Source: Ernst & Young

According to interviews, the different types and specificities of the various procedures are relatively well understood by the stakeholders. The EMEA coordination role is well recognised. As a consequence, the whole authorisation process system is better understood by the “European level” of stakeholders (see the flower in the bottom-right corner of the Figure 26) than the national level (healthcare professionals, EU citizens).

From a national perspective, room for improvement to streamline the procedures between does exist. For instance, the existence of only three procedures, covering national, transnational and Community wide levels, could simplify the global understanding of the system.

The organisation of the EMEA Secretariat itself needs to be investigated to assess whether it contributes or limits the Agency objectives through a thorough review of EMEA organisation at all levels:

- ▶ The organisation of each scientific committee and expert group;

- ▶ The allocation of tasks between committees;
- ▶ The activities performed by the EMEA Secretariat;
- ▶ The support provided by IT Systems;
- ▶ The governance of the EMEA: the management board and EMEA regulatory authorities.

The organisation of EMEA committees requires some adjustments to face an increasing workload

The composition of the committees may offer organisational alternatives between a "Member State model" including a representative for each MS and a "Expert model" based on the required expertise

NCA's are unanimous on the effectiveness of the whole Committee system with 89% of the respondents to the questionnaire considering it as being effective.

However, as mentioned above, the EMEA organisation has become more and more complex, through the addition of committees, Working Parties (WP), Scientific Advisory Groups (SAG) and other ad-hoc groups. The internal composition of each body varies and therefore impacts differently their respective effectiveness.

According to the feedback of internal stakeholders, the composition of committees, WP, SAG and other expert groups should be adapted to their respective objective, which is currently not always the case.

Two models in the committees' composition can be distinguished:

- ▶ A so-called "Member State model" with a representative for each and every Member state,
- ▶ A so-called "Expert model", in line with the expertise required for a particular committee.

Considering the high number of members and the related consequences in terms of organisation and management, the relevance of the "Member State model" as a systematic approach could be questioned.

Among the existing committees, it also appears necessary to differentiate two types of committees, with regards to their regulatory competences and opinion-making roles in the system:

- "Opinion-making committees": CHMP, CVMP and COMP, that are respectively adopting EMEA final opinions for human and veterinary medicines or orphan drug designation, directly followed by E.C. decision, and PDCO that is performing early assessment (paediatric investigations plan)
- "Pre-committees", preparing the scientific opinion that will be finally made either by the CHMP or CVMP: CAT that is respectively contributing to the assessment of specific product (advanced therapy products), PDCO for the PIP or HMPC.

Opinion-making committees

The CHMP, CVMP, COMP and PDCO are organised on the basis of the "Member State model", with 27 representatives of the EU Member States, three representatives from Norway, Liechtenstein and Iceland, and some co-opted members.

CHMP and CVMP mandates of delivering opinions for marketing authorisation as well as COMP mandate of delivering opinion for orphan drug designation legitimate the use of the "Member State

model” for the composition of these committees with the presence of the 30 Member States around the table.

All stakeholders support this statement. Each Member State is legitimate to take part in the votes; and this participation increases in return the legitimacy of EMEA opinions. EMEA opinions endorsed by a qualified majority of Member States are then followed by EC decisions that are valid in all Member States. Through their involvement in EMEA opinion-making processes, Member States remain accountable towards their citizens for highly sensitive decisions. In addition to this political aspect, Member States representation is also a means to ensure an equal access to information: the vote may be crucial, but the whole discussion behind is also of high importance. In this context, co-opted members may cover potential lack of expertise of the committee members. Committee members, especially when they act as Rapporteur/Co-Rapporteur may also be accompanied by one of their NCA's staff for his/her expertise in the needed field. The counterpart of such an organisation may be a lower efficiency as more members are involved in committees discussion than it would be theoretically required to cover scientific needs.

Newly created committee such as the PDCO has a less critical mandate in terms of regulatory competence and a more focused scope activities. Its opinions are not followed by E.C. decisions, for which it would be directly accountable. However, this committee deals with specific issues like children care that may be particularly sensitive for the public opinion. This may be the main reason why Member States are quite reluctant to give up their participation in this committee. In addition, a high level of expertises is required to deal with the paediatric development issues. A compromise might be found between the organisational “Member States model” and the expertises requirements. As suggested earlier for the nomination process, a list of required expertise could be drafted by the EMEA. Proposed Member States candidates (possibly several) would then be qualified accordingly to this list.

Pre-committees

HMPC and CAT newly created committee have also a less critical mandate in terms of regulatory competence. Its opinions are not followed by E.C. decisions. CHMP is making the final opinion. A high level of very specific expertises is required for these committees. The setting-up of the committee took into account these expertise requirements. The CAT is also based on the “Member States model”, but considering that some NCAs do not have internally advanced therapy experts, the representatives of these Member States are external experts to the NCAs. Such practices are another way to ensure the relevance of the committee composition and the related quality of their work.

In order to ensure the highest effectiveness of the Pre-committees and to achieve a high quality of outputs, Pre-committees should be composed according to the “Expert model” favouring the best available expertise.

The creation of a new pharmacovigilance body (potentially a committee) should accordingly find the right balance in terms of internal composition with regards to its responsibilities as set up in the future regulation.

Working Parties, Scientific Advisory Groups and other supporting expert groups

Committees are supported by expert groups bringing specific inputs in the assessments and committees discussions. These expert groups are not allowed to adopt any final opinion. However the access to information may still justify the direct participation of Member States in some expert groups.

Two types of working parties can be distinguished:

- “Historic” working parties, dealing with more general and widely impacting issues (Safety, Quality, Pharmacovigilance);
- Most “recent” working parties set up to answer to an increased CHMP/CVMP need for expertise. The Member States model does not necessary prevail in this case.

According to NCAs feedback, **broad impact topics should involve all Member States' representatives**. For more specific working parties, the expert model should be clearly favoured.

The scientific advice working party and scientific advisory groups, all based on needed expertise, are working well. Members, nominated according to their expertise, show a great motivation. The only limit is the independence of experts, in the strict respect of conflict of interests' procedures.

The organisation of committees, working parties and other expert groups should be clarified with respect to their objectives and regulatory competences. For each type of expert groups, the right balance between legitimacy, information of Member States and expertise coverage has to be found:

- ▶ **Opinion-making committees** are delivering opinions that are directly followed by an EC decision. As such, CHMP, CVMP and COMP require Member States representation like any EU institution, as stated by the legislation;
- ▶ **Pre-committees and working parties** might remain on the basis of the “Member States model” in terms of composition as far as the exchange of information between Member States is a priority and could be enhanced with the opening to external expert or through co-opted members. However, the effectiveness of certain of these bodies, contributing working parties, scientific advisory groups and other expert groups, might even be enhanced by using an “Expert model” for their composition when no specific political or information issue is at stake and where the science or the regulatory expertise prevails.

Tight schedules of scientific committees illustrate the limits of the current organisation

CHMP and CVMP members report that the agendas of these committees have already reached their capacity limits. Hereafter the frequency and duration of meetings is listed for each committee. With regards to the total number of weeks per year, it may be difficult to increase neither the frequency nor the duration of the meetings.

Committee	Frequency	Duration
CHMP	11 times a year	4 days
CVMP	11 times a year	3 days
PDCO	13 times a year	3 days
COMP	11 times a year	2 days
CAT	11 times a year	2 days
HMPC	6 times a year	2 days
Management Board	4 times a year	1 day

CHMP meetings take place between Monday to Thursday and from 8.30 to 20.30. In this context, CHMP members are certainly exhausted at the end of the week, raising a certain level of risk in terms of quality for dossiers considered at the end of the 4-day session. CHMP agenda is already very heavy (60 to 70 pages), and the Chair has an important role to play in order to respect this tight schedule. Considering the increasing workload, the current organisation of this committee's agenda is not perceived as sustainable. In such conditions, the enlargement of the CHMP scope cannot be considered. According to the stakeholders, the CHMP should focus on its mandate, which is to issue opinions on innovative products.

Some topics are already dealt with aside from the meeting (variations type I and II). Straightforward procedures do not come into discussion and are directly managed by the EMEA Secretariat. The CHMP committee meetings could be further streamlined in this way.

Data management and electronic tools have also been implemented to increase the efficiency of the meetings (this topic will be discussed in 5.2).

The following types of actions could be considered to limit CHMP workload:

- The creation of a second CHMP has been sometimes mentioned, but is not welcomed by all stakeholders. Other committees dedicated to a specific area are perceived as a more relevant solution. 17 out of 22 NCAs respondents consider that COMP, PDCO and CAT already contributed to decrease the workload of the CHMP, by increasing the level of expertise in these specific areas (see Figure 27).
- Another possibility would be to have two CHMP meetings a month, but the EMEA meeting agenda is already very tight.
- The solution that is mentioned the most is the creation of “subcommittees” under a pre-committee format with a consultative mission towards CHMP such as CAT, dedicated to subsidiary issues like referrals, which are often related to issues on generics.

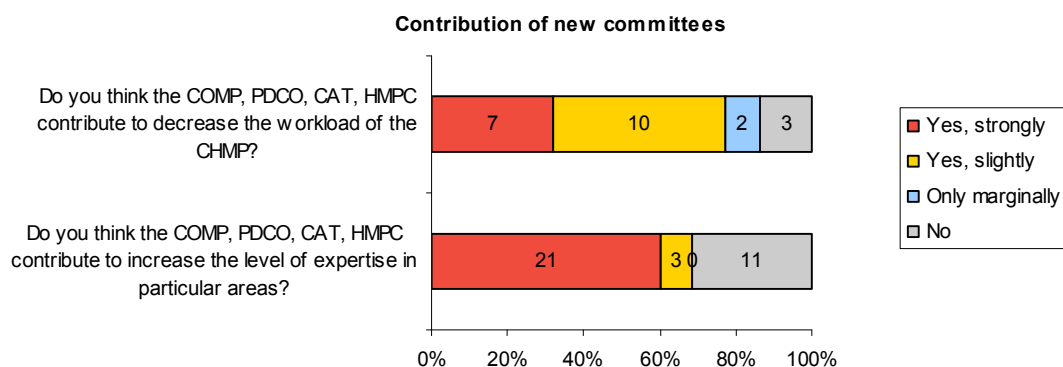


Figure 27: Questions 20.2.8 / 9 Do you think the COMP, PDCO, CAT, HMPC contribute to decrease the workload of the CHMP? / to increase the level of expertise in particular areas?

Source: Ernst & Young NCA questionnaire, June 2009

The activity of committees is supported by a limited but increasing number of Member States through various ways

The allocation of Rapporteurship and Co-Rapporteurship quantifies somehow the involvement of the Member States (this point will be further discussed in 5.2.2 with regards to the efficiency of the network), even if some contributions are not reported. The progressive learning process should lead to the involvement of more Member States in the longer term.

Between 1995 and June 2006¹⁹, 6 Member States have performed 61% of all dossiers (see Figure 28). If we extend the scope to medium contributors, 13 Member States were Rapporteur or Co-Rapporteur for 96% of all dossiers.

With EU-enlargement, new Member States expressed a need for confidence and experience in order to be able to take Rapporteurships. This transition period is not yet finished. Hungary, for instance, has taken 5 Co-Rapporteurship between 2004 and 2006. However, the availability of an increased number of experts allowed by the enlargement did not contribute to enlarge significantly the allocation of Rapporteurships to more Member States.²⁰

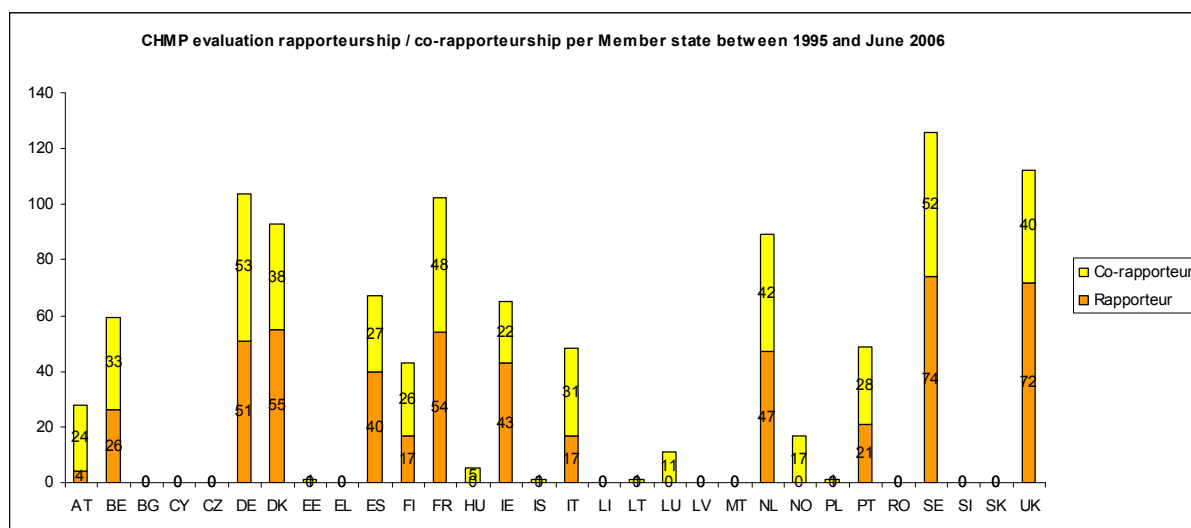


Figure 28: Member States' contribution as CHMP Rapporteur / Co-Rapporteur for products (number of dossiers) between 1995 and June 2006

Source: EMEA statistics produced for the HMA resource group

The CVMP Rapporteurship allocation process aims at encouraging a balance between Member States, taking into account the past involvement of each Rapporteur. Nevertheless, the system has not really achieved its objective, because it is based on Rapporteurs and not Member States. At the end, most Rapporteurships are still shared between a few Member States that are working with several Rapporteurs.

Most committee members recognise that a limited number of Member States are taking part in the committees' discussions. Several reasons have been pointed out including the lack of confidence, the lack of experience and sometimes limited fluency in English as a working language. At the CVMP level, some Member States never even attended to any of these meetings.

The unequal involvement of committee members may weaken the whole system. That is why consolidating the scientific expertise of NCAs and the whole network should be considered as an overarching objective of the EMEA (this point will be further discussed in 5.2). An important added value

¹⁹ Considering the difficulty for the EMEA to produce figures about Rapporteurship (Rapporteurship allocation was registered with the name of the Rapporteur and not its nationality until recently), our analyses on this topic are mainly based on statistics produced previously for the HMA resources group.

²⁰ It appears that new Member States participate in peer-reviews, PIP, guideline developments, generic-medicinal product-related and other activities).

of committees and expert groups is the stepwise international involvement of NCAs. A step by step process in alignment with delegation procedures allows building up agencies. The peer-review process and work-sharing projects contribute also to this learning process. New Member States will achieve a progressive gain of experience and confidence; and will be keen on being more involved. Some committee members already noticed an increasing involvement of their representatives (see 5.2.2 for more details and NCAs perception). Even if Member States do not take directly Rapporteurship, Co-Rapporteurship or peer-review, their contribution to the discussions is considered as very important and very useful for the Rapporteur and assessment team. This increasing involvement (however still insufficient) may also help the Chair to anticipate the results of the vote (this point is discussed later) and contribute to a manageable committee agenda.

Because of the limited participation of some Member States representatives in the discussion, the chairs of the Committees may have difficulties to anticipate the vote and its expected output. At the CHMP, orientation votes are sometimes performed in order to moderate the discussion accordingly.

Some experts fear that votes may be sometimes more based more on voting strategies than on scientific opinions. Because of personal contacts and trust or to recognised expertise, an expert may follow the vote of its neighbour. This risk has to be mitigated considering the fact that in most cases, the decisions are not highly controversial. However, it is clear that some NCAs' may have more resources available than others to scrutiny the dossiers and set up their own judgement.

Nevertheless, members from MS with little involvement mentioned that they might make up their own mind on the basis of all the briefing materials received or listened to during the discussions at the meetings. In the scientific domain, people are more used to working together, taking into account other points of view and eventually come up with their own minds. Oral explanations are also a good opportunity to understand the company's view and issues at stake.

Finally, the whole system is relying on trust between Member States representatives. Majority-based decisions (27 Member States makes it sometimes easier) smooth the general system, limiting extreme views.

The consistency of EMEA outputs relies on a proper coordination between committees, WPs, SAGs and all types of expert groups

As the EMEA complex architecture relies on strong interdependencies, EMEA takes measures to facilitate the coordination between working bodies

The EMEA activity is supported by a complex structure where the relationships between committees are a critical concern.

This system forms a nebula of about 35 groups articulated around 6 committees (see below Figure 29) with a limited number of resources. EMEA is experiencing some difficulties in finding the right balance between the appropriate coordination and autonomy of each of those groups, taking into account the specific mandate of each group, the strong interdependences connecting them and, in case there is no direct relationship between groups, the potential interactions of their outputs ensuring consistency of the whole system.

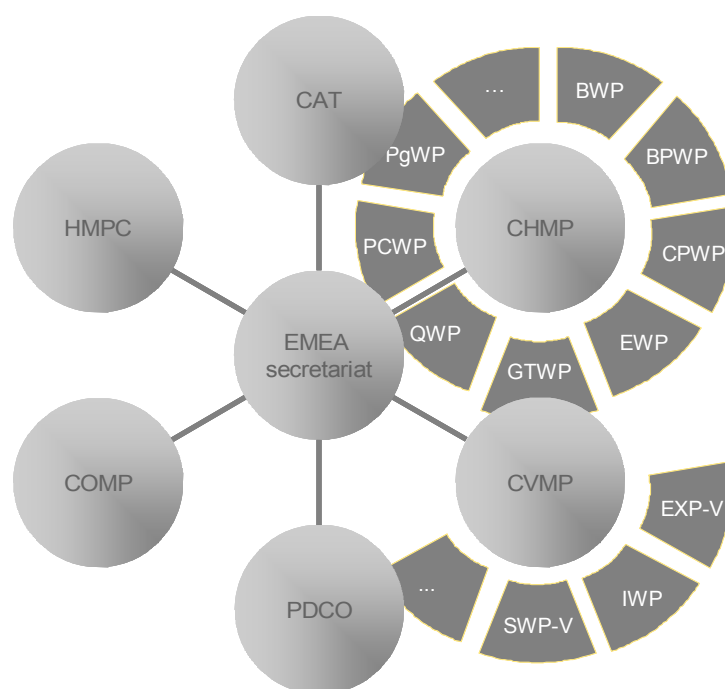


Figure 29: EMEA committees' organisation

Source: Ernst & Young

The appropriate coordination is ensured by:

► **A proper “relationship management”** whose goal is to create relationship between committees. Several instruments are at their disposal:

- Implementation of organisational guidelines:
 - EMEA policy on appropriate coordination between the scientific committees of the agency (October 2008),
 - General dealings between SAWP Secretariat and working parties, SAGs, committees and patients' organisations (January 2009),
- Appointment of dedicated responsibilities to solve some issues:
 - The position of Senior Medical Officer, directly attached to the executive director, was created at the EMEA Secretariat to contribute to the consistency and predictability of the Agency's opinion-making process (February 2007);
 - The PTL role, as mentioned already above, to ensure a continuity along the whole assessment process;
 - The Central Information Group (CIG) is ensuring the consistency of assessment procedures, from the receipt of applications to the output.
- The incentive for joint representation of members in different committees/working parties. This practice is encouraged by the EMEA, and greatly contributes to stabilise the NCAs' network, while keeping it dynamic. It is obviously limited by the capacity of an individual to be present at the different meetings inherent to its groups.

- ▶ According to the policies and the different interviews, **the chairs of the committees are playing an essential role** in this coordination exercise. Indeed, the committee management must be responsible for building strong cultures, and construct good relationships within the organisation. However, the ability of organisations to rely on leadership lead to obvious drawbacks since the success of the coordination is dependant on individuals.

However, the risk of overlaps still requires specific attention

Although the EMEA implements the right measures to maintains or improve the relationship between the different committees, some interactions, such as PDCO / CHMP, CAT / CHMP or Pharmacovigilance working party / CHMP, could be improved.

The relationships between CHMP and PDCO have been challenging and controversial. The main reason is that the regulation does not ensure the consistency between opinions of these two committees with two committees being opinion-making committees potentially for the same product at two different periods of its life-cycle (see 5.3.2 about this specific procedure). The industry outlined this situation as a specific concern. Thus, the organisation should provide effective measures to reduce the risk of incoherence between the opinions produced by the PDCO, and, later in the drug development process, by the CHMP itself, and potentially by the Scientific Advice Working Party as well.

In addition to the mentioned coordination measures at EMEA level, specific additional measures have been designed for the PDCO:

- ▶ A minimum of five CHMP members should be part of the PDCO committee;
- ▶ PDCO members are as much as integrated into other working groups as COMP members might be (according to the professional profile of the members);
- ▶ SAWP Secretariat liaises with PDCO for paediatric scientific advice / protocol assistance.

However, such organisational measures may be perceived as insufficient, notably considering the limited availability of experts.

In order to avoid any risk of diverging EMEA opinions, the legislation should clarify the status of the opinions expressed by the different committees and in particular the PDCO, the SAWP and the CHMP.

This clarification should lead to a clear differentiation between opinion-making committees (CHMP, CVMP and PDCO) and pre-committees. This will results in more transparency and consistency towards the industry.

The Committee for Advanced Therapies (CAT) is intended to play a central role in the scientific assessment of advanced therapy products. There are three types of advanced therapy products defined in the legislation: gene therapy products, somatic cell therapy products and tissue engineered products. While those categories were previously dealt with by working parties, the creation of the CAT has led to a potential duplication of work.

Indeed, some interviewees pointed out potential overlaps between the new CAT and some CHMP working parties, as the cell-based products working party (CPWP) or the gene therapy working therapy (GTWP). This point of view has been illustrated by the 2009 work plan of these two working parties (CPWP and GTWP), underlining that the risen issues “have to be adjusted taking into account the activities of the new Committee on Advanced Therapies (CAT) in 2009”.²¹

²¹ EMEA, Gene Therapy Working Party (GTWP) Work Plan for 2009 (EMEA/CHMP/GTWP/168855/2008), September 2008 and Cell-based Products Working Party (CPWP) Work Plan for 2009 (EMEA/CHMP/CPWP/319258/2008), September 2008

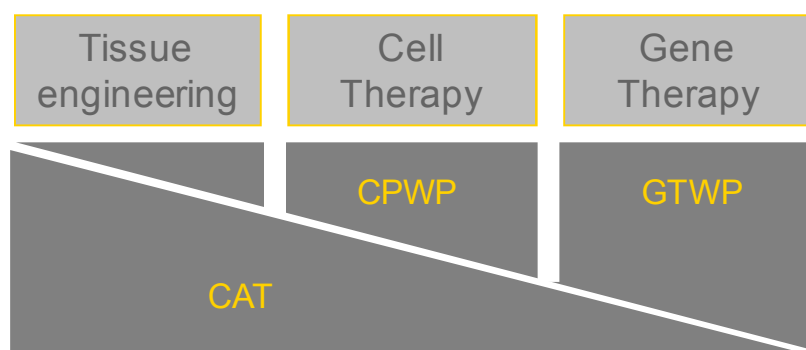


Figure 30: Potential overlaps between CAT and CHMP working parties

Source: Ernst & Young

More generally, a regular review of working parties should be initiated, in order to clarify their respective mandate and to increase their flexibility.

Working parties are theoretically created to answer a specific and temporary issue. EMEA has currently 25 working parties, plus 8 scientific advisory groups and 4 other associated groups. Some of these groups may be less relevant in supporting committees considering the development of the EMEA organisation and the scientific research development. EMEA may develop the ability to both create and remove a working party when appropriate.

In the current organisation, the relations between the pharmacovigilance working party and the CHMP are clearly established, considering the different status of both bodies. The pharmacovigilance WP is able to express diverging opinion on the basis of safety considerations, however the CHMP remains the opinion-making body based on the whole risk-benefit assessment.

The 2009 CHMP work programme considers the interaction with the Pharmacovigilance working party and delegations as a high priority. This issue will become more and more critical with the expected new pharmacovigilance regulation (see 5.3.4).

On the whole, the EMEA seems to be fully aware of such organisational risks, as important efforts are being undertaken to solve potential overlaps.

Since 2006, the EMEA is undertaking a wide process improvement exercise, looking at various key processes managed at the EMEA Secretariat level. The aim of the exercise is to increase efficiency in operation, avoid duplication of efforts and improve teamwork.²²

The 2009 CHMP work program identifies also projects requiring specific attention in terms of internal coordination such as:

- The revision of role and mandates of WP;
- The paediatric regulation and PDCO/CHMP interactions;
- The optimisation of the consultation processes of SAGs and Specialised Experts groups.

²² EMEA, Second status report on the implementation of the EMEA Road Map, October 2007

The more EMEA committees and expert groups will differentiate their scope and responsibilities, the more there is a need for integration and coordination of work activities. This coordination and integration is mainly achieved through the human resources organisation as well as some guidelines for interdependent work activities. Nevertheless, the IT network also plays an active role. It helps to manage cross committees' processes more smoothly (this point is further discussed in a following paragraph).

The EMEA Secretariat support

The role of EMEA Secretariat has strongly evolved from an highly appreciated administrative and regulatory support towards a two-dimension support with more and more scientific support on targeted areas

The effectiveness of EMEA Secretariat administrative and regulatory support is highly appreciated. Since its creation in 1993 and its further strong evolution over time, the main role of the EMEA Secretariat has been to provide scientific committees with administrative and regulatory support.

In this respect, **all stakeholders have shown a great satisfaction towards the administrative and regulatory Secretariat support.** EMEA staff is perceived as very professional and highly qualified. NCAs recognise and appreciate the support of the EMEA Secretariat mainly in the three following fields:

- Secretarial and preparatory work;
- Coordination of assessments and inspections;
- Regulatory inputs.

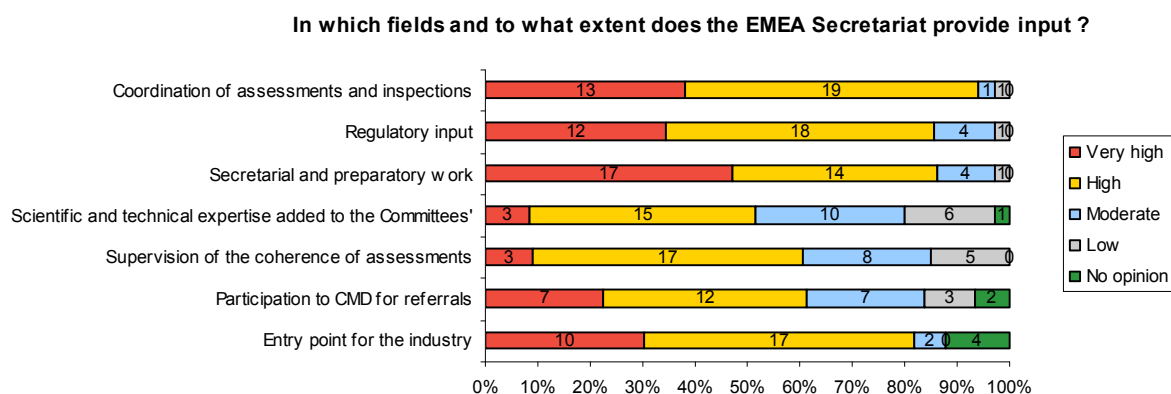


Figure 31: Questions 21.2 In your opinion, in which fields and to what extent does the EMEA Secretariat provide input?

Source: Ernst & Young NCA questionnaire, June 2009

EMEA Secretariat concentrates its efforts to make experts' life easier, especially by taking care of procedural issues or by providing documentation. NCAs experts can then concentrate on scientific issues.

However, some room for improvement has been identified by NCAs with regards to these support activities:

- EMEA Secretariat does not cover all administrative work induced by a Rapporteurship, (e.g. database to follow the authorisation process and the planning of all tasks), which can be an issue for small agencies lacking of resources but willing to take Rapporteurship;
- EMEA support should focus on particularly appreciated area: regulatory control, drafting of proper documentation in good English wording;
- Some NCAs would like to have more support from the Secretariat with regards to the

communication to the industry and patients: the EMEA could be more involved in drafting communication briefings.

As foreseen by 2005 regulation, the Secretariat has progressively provided more scientific assistance to committees, notably to meet the needs of some NCAs.

With the new committees (COMP, PDCO, CAT), the Secretariat is even more involved in terms of scientific support: the EMEA is contributing directly to the assessments as coordinator for the orphan and paediatric committees. In addition, NCAs and EMEA inputs appear to be complementary.

EMEA contributions for these newly created committees are **highly appreciated by NCAs experts**. This contribution is also a convenient solution, notably to face the lack of resources of some NCAs.

EMEA staff members are very keen on following this evolution; therefore they often have scientific backgrounds. The EMEA recruitment policy has also been adapted towards the new areas of expertise.

Although the EMEA Secretariat is developing its evaluation activities progressively and very carefully, some NCAs have expressed their apprehensions regarding this trend: **one third of NCAs express a negative opinion regarding the reinforcement of EMEA support**, 46% being in favour (see Figure 32 below).

Do you believe the Secretariat's support should be reinforced?

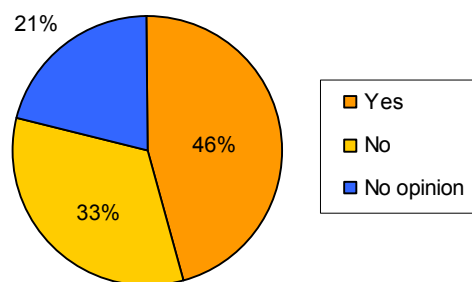


Figure 32: Questions 21.3 Do you believe the Secretariat's support should be reinforced?

Source: Ernst & Young NCA questionnaire, June 2009

Indeed, the increasing scientific role of the Secretariat could be conflicting with the prerogative of the Member States. The contribution of the EMEA in the assessment of dossiers for the centralised procedure is recognised as very useful on specific part, for example variations, but NCAs consider the Secretariat as less legitimate than NCAs experts on Rapporteurships. In addition to that, the EMEA Secretariat may not have the available expertise in all required areas.

However the enlargement of EMEA Secretariat's scope of activities highlights the trust of Member States in its organisation and experts. *One of the interviewed CVMP members considers the EMEA as very efficient in the realisation of its goals. As a lecturer on the management of organisations and theories of leadership, the interviewee has identified 3 key factors for efficient organisations that are fulfilled at the EMEA:*

- *Good structure,*
- *Good procedures,*
- *Well-educated people.*

Ensuring consistency of opinions remains a key task for the EMEA Secretariat either through internal procedures as a proper framework or through NCAs training

Considering the whole organisation of the European authorisation as a network, one key task of EMEA Secretariat is to coordinate the European NCAs properly, and at the end **to ensure the consistency of outputs** produced by these various stakeholders.

More generally, the role of the EMEA Secretariat is to point out the discrepancies and issues related to opinions for similar subjects issued by different experts or at different times. As being the central coordinating body, the EMEA acts indeed as a **scientific and regulatory memory** and is responsible for ensuring a consistent regulatory philosophy across EMEA's area of activities and times.

EMEA procedures are designed to ensure consistency between scientific opinions produced by the assessment teams. The peer-review team is for instance composed by one reviewer from the Committee and one reviewer from the Secretariat, addressing particularly the reliability and consistency of the opinions.

Consistency of opinions is a sensitive issue for the industry (refer to the answer to the first evaluation question) and NCAs experts. Actually, some NCAs are in favour of an even stronger involvement of the EMEA Secretariat in the network, by facilitating the work between the teams.

National experts identified another key added value of the EMEA organisation as facilitator. Considering potential movements within NCAs, the EMEA Secretariat is able to **secure knowledge and competencies** when people leave the NCAs. The risk of losing expertises to the benefit of the industry is very acute in specific areas, for example like advanced therapies.

To some extent, the EMEA recruitment policy should be considered as a way to compensate the NCAs structural weaknesses in terms of expertise.

Another way for the EMEA to ensure consistency between assessments is to encourage the use of a common assessment methodology by Member States. EMEA guidelines are providing NCAs with some guidance, but further support measures are required to reach common understandings among Member States. In this respect, one of the requests addressed by NCAs to the EMEA is to further develop training for assessors. 87% of NCAs consider trainings as an important to very important benefit provided by the EMEA (see Figure 31). Indeed, such trainings are of high importance, especially for small and/or new Member States, to help them to improve their assessment methodology.

EMEA trainings should be further developed, in order to meet NCAs expectations and to allow a broader involvement of Member States in assessment work (see 5.2.2).

According to their feedback, training for assessors should focus on practical case studies. NCAs would like to receive “on the job” training about quality and clinical assessment in addition to the EMEA guidelines. Another aspect NCAs would like to get trained on is IT.

EMEA internal organisation has to cope with the risk of a growing complexity

Following the enlargement of its scope of activities, the EMEA Secretariat has adapted its internal organisation (this point is further discussed later in the report). Like any other organisation facing internal growth issues, the EMEA Secretariat had to address the growing complexity of its organisation.

The on-going reorganisation, dated September-December 2009, aims at improving use of resources, addressing the challenge of administrative simplification. Several organisational measures have been taken:

- Pre- and Post- Units are merged in a single unit to better structure the authorisation process according to the product life-cycle;
- Pharmacovigilance activities are also reorganized towards an integrated life-cycle management, i.e. taking into account pharmacovigilance issues before the authorisation.

- An entity is created focusing on product data and knowledge management.

Such measures are trying to overcome the mature organisation classical trend towards silo-thinking between units.

The role of the Product Team Leader (PTL) was initially designed to ensure continuity in the relationship with the applicant. This is clearly meeting the needs of the industry. However, some complaints have been expressed that should be taken into consideration to ensure greater quality of the support, in particular:

- PTL may deal with a too high number of products;
- The quality of support provided can substantially vary from one PTL to another. The industry may prefer to work with scientifically experienced PTL rather than regulatory experienced ones;
- PTLs' turnover may impact the quality of the relationship with the industry;
- Finally, the industry is asking not only for simplification, but also for greater transparency regarding the role of the different EMEA Secretariat units they are working with.

The EMEA IT systems provide NCAs with useful support

Electronic tools and databases highly contribute to the benefits provided by the EMEA for NCAs: 62% of the respondents to NCA questionnaire consider it as very important and one additional third as important (see Figure 31).

Two types of IT systems have to be distinguished:

- ▶ IT tools supporting EMEA meetings and expert works;
- ▶ EMEA databases (so-called Telematics), allowing the storage and exchange of data between Member States.

IT-tools facilitate the organisation of meetings and expert works

NCAs consider teleconferencing tools as a mean to travel less and to improve efficiency. However, NCAs experts identify room for improvement with regards to e-collaboration tools. Technical systems for teleconference are still not harmonized across Member States. Some NCAs are still using old technologies and the EMEA is also using different systems. The poor quality of transmission has a great impact on the quality of the exchanges between experts.

EMEA Secretariat should therefore promote the use of a single teleconference system, like Vitero which is the NCAs experts preferred system. Technical standards should be also promoted for a proper use of teleconference systems.

Telematics allow data storage and exchanges between Member States and has developed towards greater coordination and a more consistent European IT architecture

The EMEA Secretariat has the important function of being responsible for pan-European databases, Telematics that rely on data provided by the Member States. NCAs consider Telematics as very important with respect to the rapid exchanges of information and the creation of valid databases for the Member States.

As an interviewee pointed out, EMEA IT support is highly appreciated,: *“We use all the tools and databases in everyday work. In our national database making process, we legislate for EMEA database terminology and principles to assure compatibility with EMEA.”*

EMEA systems are used by NCAs and generally considered as properly working, with slightly different perceptions between the systems. The perception of benefits provided by telematics to NCAs is synthesised hereafter, but their functional utility and weaknesses will be further discussed in respective paragraphs (see 5.3). Telematics costs will be discussed in greater details in paragraph 5.2.1).

EudraVigilance

EudraVigilance is appreciated by certain small NCAs, making their work easier. It also aims at helping the better distribution of the pharmacovigilance information among Member States. However, experts points out the number of duplicates and inconsistent datasets as a major limit of the current system (see 5.3).

EudraPharm

Stakeholders are more critical towards EudraPharm. This tool has a very high ambition of collecting information on all medicinal products distributed across Europe and includes the information contained in the summaries of product characteristics, the patient or user package leaflet and the information shown on the labeling. It is currently dealing with centrally authorised products, but is aimed at covering all products in all European languages. This can be useful in terms of information sharing, inspections and costs reductions. However, full benefits will be achieved, **only when all tools and databases** will be fully functional at Member States' level (a memorandum of understandings has already be signed by some Member States).

Besides, the added value of such a tool for European patients (see 5.3) can be questioned with regards to the induced costs. A feasibility study launched by the EMEA should take into account all types of costs: development, training, assistance to Member States and maintenance costs.

EudraGMP

This system related to Good Manufacturing Practices is particularly appreciated by small countries that may not have such databases in-house. It offers an overview of all inspections performed by NCAs.

EudraCT

Despite its long development process, EudraCT is meeting NCAs needs, notably with the planned introduction of the data warehouse functionality.

NCAs are globally satisfied with the support provided by Telematics. However, Member States' involvement in the development of the databases could be improved to ensure consistent transfer of data.

Telematics have strongly structured EMEA IT strategy until 2008. Since 2008, a new orientation has been set up towards greater coordination and a more consistent EMEA IT architecture.

The identified weaknesses of telematics have proved the necessity of an improved coordination between EMEA and NCAs IT strategy. Furthermore, Member States' influence on the IT global architecture is crucial and should be ensured.

EMEA governance bodies should reinforce their strategic inputs

European regulatory authorities aim at achieving two different objectives, the harmonisation of the internal market and the protection of public health

Some stakeholders are concerned by the governance of the EMEA at the European Commission. More particularly, the supervision of EMEA by the Enterprise Directorate-General (DG Enterprise) is interpreted differently by various stakeholders.

Consumer organisations ask for a stronger link between the EMEA and the DG SANCO, with regards to the governance of medicines regulatory agencies in the Member States that are often under the authority of the Ministry of Health.

However, most stakeholders acknowledge the clear objectivity and quality of EMEA opinions (see section 4.1.1). The EMEA is firstly a regulatory agency issuing scientific opinions. The participation of the European Commission in scientific committees is sometimes criticised in this extent. It seems that this may be due to a misunderstanding of the Commission's role in the opinion-making committees: critics may not be aware of the fact that EC representatives do not vote. However, the Commission presence may be legitimate in case of arbitrations regarding different interpretations of European directives. In addition, health issues mainly remain a competency of Member States.

In the system of European agencies network, the EMEA has to be administered by one Directorate and one funding section.

Nevertheless, the EMEA has to find the right balance between European market issues and public health considerations. At the governance level, the double authority DG Enterprise – DG SANCO is trying to ensure the respect of both objectives, a proper functioning of the internal market and the protection of EU public health. At the operational level, the EMEA is developing close interactions with both industry and patients organisations.

The Management Board, aiming at ensuring the representation of all EMEA regulatory authorities, is not sufficiently involved in strategic issues

The EMEA Management board is composed of representatives of the European Parliament, the European Commission (both DG Enterprise and DG SANCO) and of each Member State. Representatives of the civil society (patients, doctors and veterinarians organisations) are also members of the Management Board. The board meets four times a year during one day.

Consequently, some stakeholders fear that veterinary interests are less defended compared to human medicinal products, given that representatives of Member States at the board are mainly heads of human agencies.

The EMEA roadmap is proposed by EMEA Secretariat (under the responsibility of the executive director) and then approved by the Management Board. The Board is also consulted on the nomination of committee members by Member States. However, regular activities of the Management Board deal more with reporting analyses presented by the EMEA Secretariat than with strategic issues. This may be due to the size of the Management Board (35 members) that may not be convenient for strategic discussions. The Management Board has a system of topic coordinators: for a number of topics (e.g. when preparing strategic documents, budget, work programme, various policies, etc), a group of members is appointed. Conclusions are then presented to the Board.

Some stakeholders from the NCAs would prefer a greater involvement of the Management Board on strategic matters. The agenda or the organisation of the work could be adapted to focus on such issues as future developments of EMEA activities.

The question of EMEA governance is examined more in-depth by the study launched by DG BUDGET in 2009 on EU decentralised agencies. This evaluation covers the 26 agencies and is focusing on the budgetary governance and the monitoring of the Community mandate. The conclusions of this study could help to identify some good practices among other European agencies.

The HMA is the network that consists of the Heads of NCAs in the European economic area. This network has been set up by NCAs on a voluntary basis, without the umbrella of the European Commission.

The relationships between the EMEA and the HMA contain another area for improvements. HMA and EMEA are both based on the contribution of NCAs and duplicate working groups may exist (for example telematics). The risk remains quite low though, as members of both groups are most likely to be the same experts from the NCAs. However the coordination should be ensured at a higher level.

There should be more interactions between HMA and EMEA and the Management Board should act as a natural link between them.

5.1.4. To what extent does EMEA organisation address the recent and future contextual challenges?

The organisation is constantly adapting to the increasing qualitative and quantitative demand

The raise of the workforce is strategic to adapt the increasing demand

In this chapter we have observed that EMEA has been under pressure of an increasing demand in the recent years. Various reasons, explaining the increasing demand faced by the EMEA, are explored throughout this report. These include, in particular, the progressive extension of scope of the centralised procedure, the increase of generic applications for the centralised procedure, as well as the increase of referrals for veterinary medicines and the EU enlargement. The adaptation of the EMEA to this rising demand is a serious challenge. Indeed, in the public health domain, this challenge must reconcile contradictory aims of maximising the quality of the activity while guaranteeing the sustainability of the system with limited resources.

Although quality and quantity of outputs tend to improve, it is possible that EMEA will face difficulties coping with the increased demand in the near future, especially since many stakeholders express doubts on the sustainability of the system as it is currently (see the sections 4.1 and 4.2 on efficiency and NCAs involvement).

There are multiple options to adapt to the increasing demand, both qualitatively and quantitatively:

- ▶ Adapting the resources to the qualitative needs: EMEA has established new working parties, SAGs and committees, such as the CAT, to adapt to the qualitative evolution in demand, i.e. the evolution of science in this case. As discussed in section 5.1.3, the CAT is considered as an important improvement in EMEA ability to deal with advanced therapies. However, it is also important to bear in mind that SAGs are supposed to have a transient activity, to answer specific problems. Some careful approach needs to be taken in relation to the current needs regarding SAGs and working parties, to avoid unnecessary solicitation of the workforce and to allow for a more efficient system.
- ▶ Alleviating the CHMP/CVMP workload by redistributing the evaluation to specific sub-committees: this option is discussed in various parts of the report. As discussed in 5.4.4, one of the most mentioned causes for increased demand is the increasing proportion taken by generic medicines in the evaluation, as well as the concerns related to referrals (examined in 5.1.2). Thus, allowing these activities to be delegated to specific sub-committees, under the final authority of CHMP (respectively CVMP) may be a way to facilitate CHMP (respectively CVMP) activity and allow them to focus mainly on the evaluation of innovative medicinal products.
- ▶ Increasing the outputs by improving the efficiency: this topic is largely discussed in part 5.2.1. For some activities, it is perceived that the pursuit of efficiency has reached its limits if resources are not increased (for example: the CVMP has recently informally refused a referral for a class of generic for the first time, and asked the Commission to split the dossier in smaller and more manageable files).
- ▶ Increasing the output by extending the resources: the workforce must be sufficient in number, have the appropriate education and be adequately trained and motivated. As we will see in the following chapter, although EMEA Secretariat has significantly increased its resources in the past 5 years, the same cannot be said of the NCAs, which may punctually lack the resources for evaluation assessments and some of which are concerned about their ability to procure the system with the right amount of resources if the demand continues to increase.

But the shortage of qualified workforce is a European issue, and impacts both NCAs and EMEA Secretariat recruitment

Most recruitments at the Secretariat level taps into a pool of resources that could also partially be used by NCAs. Some agencies have feared that the EMEA may attract some of their best resources because it can offer interesting employment conditions. Although such a turnover between NCAs and EMEA is wished for, as it allows for a better circulation of competences, it also raises the issue of the limited number of qualified resources throughout the EU, especially in some small and/or new MS. Thus, if we consider the Agency as whole (Secretariat and NCAs), the pool of resources is not indefinitely expandable, as long as no specific effort for training is made at the national levels. Unfortunately, the European shortage of human resources for healthcare and science activities is already identified as a main challenge by various actors of the sector (see report “Human resources for health in the WHO European”, 2006, World Health Organization).

Thus, the problem is a general problem that should be addressed by governments and policy makers. It requires a proper human resources management at the EU level, and in particular an adequate analysis of the staffing needs per area. At the Secretariat level, the establishment of multi-annual staff policy plan is an example. A coordinate effort among countries to harmonize training between Member States (included, but not limited to, English teaching for example) must then be promoted by adequate policy makers. Some NCAs also have insisted on the importance of sharing good practices, exchanging staff and facilitate multi-national assessment teams. All these initiatives should facilitate the advancement of less experienced agencies, as well as promote trust between agencies and set appropriate standards throughout the EMEA system. They should also allow the organisation as a whole to increase its efficiency, by multiplying the number of competent assessors and allowing for the best team to be used, even if such a team is spread across various agencies. The BEMA (BENCHMARK of Medical Agencies) initiative also contributes to these goals. The issues of shared training and multi-national assessment team (including logistics and distribution of fees amongst multiple agencies) are explained in more details elsewhere (part 5.2).

The EMEA organisation has to this point appropriately adapted to regulatory evolutions.

The recent Regulation (EC) 726/2004 in 2004 has brought changes in many domains that EMEA had anticipated or attempted to implement. EMEA ways of implementing this regulation have been discussed in various parts of this report. Main recent evolutions since 2000 include the extension of the scope of centralised procedure, including the possibility of submitting generic applications, the creation of novel Committees (CAT, PDCO, COMP), or the strengthening of EMEA authority on post-authorisation activities (for example, under the new law, the EMEA has the possibility to give financial penalties to pharmaceutical companies in case of non-adherence to the legal obligations). These evolutions are dealt with in (sections 5.3 and 5.4), but it can be generally noted that EMEA has deployed adapted means of dealing with regulation evolutions, including diversifying the activities of sectors at the Secretariat level, promoting communication with the industry through workshops and InfoDays, putting in place specific work programmes for each novel activity, etc.

Generally, most stakeholders agreed that EMEA adapted well to the challenges brought by the legislation. Some stakeholders even suggest to extent the scope of products under the centralised procedure. Difficulties remain with the most recently created committee, especially the PDCO, but this may be explained by an undergoing learning process.

The ability of the EMEA to adapt to the legislation change relies on its ability to anticipate the scientific evolution

The capacity of the EMEA to adapt to the legislative evolutions has depended and will depend on its continuous ability to foresee the environmental (enlargement, public opinion ...) as well as scientific trends, while keeping in line with the existing legislation. As a matter of fact, the environmental pressures together with the scientific advancements significantly impact the legislation development, although they are not the only factors.

As a scientific agency, the EMEA should mainly focus on anticipating the scientific trends, while adapting to the legislation (which integrates any relevant societal trend). Consequently, the ability of the EMEA to adapt to future legislation could be judged on its capacity to analyse scientific information, and anticipate the needs that may arise from those scientific developments.

However, in specific cases that relate to its main objectives, EMEA may also anticipate societal trends. For instance, as EMEA is expected to contribute to all European citizens' access to safe, efficient and quality medicines, it should probably anticipate the increase of elderly citizens proportion in Europe and begin discussing the topic with the Commission and other relevant stakeholders, to consider whether specific organisation adjustments should be considered (as the creation of PDCO to acknowledge the specific needs of children for medicinal products). Indeed, some discussions regarding this topic are currently undergoing at the Commission and EMEA levels.

On this aspect, EMEA has conducted numerous activities to anticipate the scientific research. For example, a series of meetings have been organised by the EMEA with individual pharmaceutical companies and academic groups to identify scientific bottlenecks to the development of innovative medicines, both in the industry's R&D and in the academic environment²³. Not only is this tripartite approach (industry, government, academic) appreciated by the various stakeholders, but this kind of dialogue is surely the best organisation to appropriately address the future challenges.

Major expected or undergoing evolutions in terms of science include the emergence of biomarkers and theranostics (i.e. the combination between a specific medicine regimen and the appropriate diagnostic device to monitor such regimen). Regarding medical devices or *in vitro* diagnostic, there are ongoing discussions to evaluate the relevance of including their evaluation into the scope of EMEA competencies. Some argue that EMEA should get involved in the evaluation of medical devices, especially since medical devices and medicines tend to get closer with the emergence of biomarkers and theranostics. This is critical because the current level of expectations towards medical devices in the EU (CE mark) significantly differs from the level of expectations towards medicines, both at the safety and efficacy levels. This debate is also of particular importance when considering nanomaterials applied to medicine.

The methodology to evaluate medical devices also differs from the one used to evaluate medicines. Thus, at this stage, the EMEA is not suited to perform evaluation of all medical devices. Nevertheless, it could contribute to define the barrier between the medical devices and the medicines. On a long term basis, one could also explore the possibility of having the EMEA acquire the appropriate expertise and extend its network in such a way to be able to perform such evaluations.

The European Commission has published a public consultation document regarding the recast of the Medical Devices Directives. It aims to standardise the different legislative frameworks across the European Member States. Such a standardisation could be a first step towards a better harmonisation between the evaluation of medicines and medical devices at the European level.

Other future evolution in terms of regulation may concern the scope of activities of the EMEA. Indeed, beyond the possibility of considering Medical Devices evaluation under the scope of EMEA, which is still very much debated, another topic which has been repeatedly raised is the harmonisation of clinical trials at the European level. At this stage, clinical trials can not be fully harmonised at European level. In some European countries, companies need to submit specific demands for each country where a centre of clinical trial is located or even to each ethic committee. There is no centralised application for clinical trials at the European level. This was for instance raised as a point of concern for FDA evaluators, as minor but challenging differences between all European national clinical trial's practices may occur leading to a limited level of "trust" in some clinical trials versus others depending on the country where the clinical trials have been performed. Although there is still space for an appropriate discussion

²³ See various reports from the "EMEA/CHMP-Think-Tank Group On Innovative Drug"

regarding this topic at the Commission level, EMEA can in this case be considered as disposing of most relevant expertise to perform evaluation of clinical trials applications according to the most harmonised guidelines.

The organisation adapts to the enlargement in order to maintain a high level of effectiveness

While the EMEA had to deal with significant changes in the legislation, it also had to face a major enlargement of the European Union (10 new members in 2004).

According to various stakeholders, and in particular the interviewed NCAs, the EMEA has successfully integrated the new members without decreasing the quality of its outputs. As an example, the timeline of the centralised procedure has not been increased with the enlargement of the EU.

Various initiatives have contributed to this achievement. For instance, key cooperation activities are ongoing to help the regulatory authorities of Croatia, Turkey and the former Yugoslav Republic of Macedonia prepare for integration into the EMEA upon the eventual accession of these countries to the EU²⁴. Another example is the shifting from two representatives per Member State to one representative (with an alternate) in the EMEA Management Board and scientific committees since the 2004 enlargement. At the committees level too, alternates are not expected to be present at every session when they do not act as Rapporteurs and coordinators.

On the other hand, most stakeholders agreed that the complexity of the opinion making process increased with the entry of novel Member States. More particularly, some criticised the unequal involvement of Member States representatives in operational activities even though all contribute equally to the opinion making process. These stakeholders went on to propose measures to weight votes differently (taking into account the size of the market, the expertise of the country on a given subject...), or to reduce the number of voters according to their involvement, or their expertise in the therapeutic area concerned by the decision. These measures are expressed as a means to improve the reactivity of the decision process. However, a majority of concerned stakeholders agree that, at least at the level of the main committees (CHMP and CVMP), the representation of all Member States must be assured, as decisions taken have a major impact at national level in terms of public health and national interests. This is in line with the current legislation. Thus, a better way to adapt to enlargement is to deploy initiatives intended at enhancing Member States involvement as much as possible, rather than excluding some Member States of the decision process.

The organisation adapts to the evolution of public expectations in terms of information and transparency

European citizens, as well as other stakeholders, are likely to expect more transparency in the future. A more transparent market in healthcare allows the patients to make a finer choice of medicines. It also gives an opportunity for the public to correlate the quality received with the relevant price, and it may ultimately enable to get better quality care for a lower cost.

Paragraph 5.3.5, is evaluating to what extent the EMEA is contributing to better information to EU patients. It also suggests some recommendations to improve the current situation. Since the communication chain gains in efficiency when passing through the NCAs to attain the appropriate public, the suggestions stress the necessity for the Agency to ensure that a NCA can appropriately transmit the EMEA communication items to their respective citizens (messages in all languages, ...) and ultimately give better access to the existing information (EPAR, ...).

²⁴ EMEA annual report 2008

In the future, citizens will increase their expectations towards transparency, while looking for straightforward access to this information. So far, the EMEA impacts the quality of the information, but is not in a position to centralise a common message regarding the use of a medicine.

For example, HMA and EMEA certainly bring different and complementary point of views regarding the use of medicine. However, even though HMA and EMEA tend to collaborate more, their structure, as well as their scope of activities, are and should remain different. While their communication towards the same stakeholders should differ from one another, both structures should coordinate their efforts, and define carefully the kind of information that should be posted by each. Indeed, from the patient's and healthcare professionals' perspective, the goal is to understand which medicine provides the best benefit in a given situation. HMAs and EMEA communication should thus contribute in a coherent way to inform citizens and healthcare professionals regarding this issue.

As the regulatory system progressively includes more partners (EMEA, HTA, EEA ...) and the demand for information increases, there will probably be a need to coordinate communication efforts between these partners. This would facilitate the understanding of the relevant issues at the patient level. One could even suggest a reflection regarding the appointment of a "communication leadership", or at least the setting of communication standards and a clear description of each partner's roles and responsibilities regarding communication, so as to avoid any incoherence and/or lack of information when browsing all medicine-related regulatory messages.

This project must be further investigated and lead to a suitable system to answer the increasing expectations of citizens in terms of transparency. It could be implemented through different measures:

- ▶ Appointment of an entity (private or public) to coordinate the different messages, and standardise them in a suitable format for the public,
- ▶ Standardisation of the communication format across agencies.

At EMEA level, this long term project will go through a rationalisation of its own communication system within the secretariat. There are currently three sectors having communication activities: executive support, medical information, document management and publishing. Although their responsibilities differ, some activities are overlapping. A common leadership will contribute to improve, or at least ensure the consistency of the messages given to the public.

5.2. Efficiency

*To what extent has the EMEA, as a part of the European medicines network, contributed to an **efficient system** of authorising human and veterinary medicinal products for the EU?*

Summary

The EMEA is composed of the EMEA Secretariat and a network of 44 National Competent Authorities. Its functioning is based on a **volunteer contribution of those NCAs**. The NCAs take part in EMEA activities through several channels, of which Rapporteurship is the most important one and the one that consumes the most resources.

The operational efficiency of the whole system (EMEA Secretariat and NCAs) has improved over the period 2000-2008.

- The EMEA core activity has doubled (from 60 initial applications for human and veterinary medicines in 2000 to 119 initial applications in 2008). The EMEA budget has followed the same trend (led by industry fees that represent on average 66% of EMEA resources);
- Although the system has become more and more complex (enlargement, extended scope of the regulation, etc.), the quality of the work has been maintained.

This point of view is also highlighted by the European Court of Auditor in 2008 special report where it is stated that “the agency was found to be performing above par”.²⁵

The evaluation identified **some specific tasks** where this efficiency gain is obvious:

- The costs of processing initial applications have followed the increase of the applications although they require to manage 30 Member States sitting around the table;
- Some activities such as orphan designation or post-authorisation activities are demonstrating signs of cost-efficiency. More generally, in almost all EMEA areas, the volumes of activities have increased more than the workforce did.

Regarding **other costs**:

- Efficiency gain has been also identified on administrative support whose costs represent less in the total EMEA budget in 2008 than in 2002 (12% versus 18%);
- However, fixed costs increased fourfold over the period whereas application costs only doubled, main contributing type of expenditure being data processing.

Cost optimisation is an on-going process within EMEA Secretariat and participates in maintaining the costs. EMEA Secretariat:

- has put in place a precise cost monitoring system to follow, on a analytical basis, the costs incurred by each its activity;
- encourages the development of long-distance collaborative tools (still too weak for lots of stakeholders);
- and it promotes paperless authorisation process.

Despite the above mentioned points, the evaluation is not able to conclude on the global efficiency of the system. A clear opinion on the total cost of the system is not possible at this stage. **Most of the NCAs have no insight into their own costs**, neither the costs of the national procedures, nor the costs of their

²⁵ European Court of Auditor, Report on the annual accounts of the European Medicines Agency for the financial year 2007 together with the Agency's replies (2008/C 311/05), December 2008

contribution to EMEA. An on going study aims at identifying the real costs incurred at national level.

The involvement of the NCAs in EMEA activities varies, depending mainly on their size, type of expertise and financing model, resulting in the fact that **seven Member States are taking 75% of rapporteurships and co rapporteurships of the CHMP.**

- Large agencies dedicate up to full-time experts to EMEA activities;
- Some medium Member States agencies are highly involved despite limited resources;
- Small agencies may not be able to ensure proper involvement in EMEA activities (e.g. some small NCAs are even rarely taking part in the CVMP meetings). Therefore these agencies limit their involvement to selected expertises such as quality as well as therapeutic areas.

All agencies consider that their involvement in EMEA activities is of high scientific interest, also to the benefit of national procedures. They also take benefits from electronic databases, interactions with the industry and personal relationships with European colleagues.

NCAs are of the opinion that **their contribution to centralised applications is mainly covered by the compensation paid by the EMEA** (50% of the fees paid by the industry), even if this compensation is barely considered as a decisive incentive to take Rapporteurship.

However, despite some differences based on their internal resources, all **NCAs are facing an increasing lack of resources** that impact directly their level and type of involvement in EMEA activities:

- They refuse to take Rapporteurship or to participate in working parties;
- They ask for the participation of external experts;
- They can not afford to maintain their involvement on non-fee paid activities.

In this context, the maintenance of the voluntary system still provides the flexibility required and the great majority of NCAs do not plan to reconsider their involvement in EMEA activities, identified as a priority for national agencies. However, its sustainability in the future is not ensured.

EMEA is indeed **for 66% financed by fees paid by the industry**. The European Commission subsidy is a balanced subsidy expected for some expenses for which an EC earmarked contribution comes in addition (Orphan, IT projects). The budget process thus allows the EMEA to cover its needs, even if the real costs supported by NCAs are not known.

In this respect and to ensure the sustainability, **some clarifications and changes are necessary:**

- The **financing of non-fee paid activities must be clarified**: a targeted compensation of the latter should be envisaged, either at European level or at national level. Both require a strong political re-engagement of the Member States;
- **Alternative types of work sharing** may be considered: on a short-term period, through the setting up of international team for instance; on a longer-term, through a balanced allocation of tasks between the Member States (that requires first supporting the development of new Member States regulatory competences);
- The development of e-collaborative tools which requires both a commitment by NCAs to have greater uptake of existing of existing remote working tools and a commitment by the EMEA Secretariat to ensure reliability and availability of these tools;
- An increase of EMEA Secretariat support despite the reluctance of some NCAs.

5.2.1. Costs of EMEA activities and outputs

This part attempts to assess the costs at which the EMEA is producing its outputs. A cost-efficiency analysis should be considered carefully. Striving for unreasonable efficiency targets may impact the quality of EMEA outputs. The analyses provided here are thus conducted on activities where being more efficient is possible without damaging the quality of EMEA opinions. Administrative costs are an example. The EMEA capacity to face an increasing workload in a context of constrained public resources has also been challenged.

Follow-up and optimisation of the costs have been put in place in the past few years

The EMEA has established a long-term strategy which aims at maintaining its efficiency (see the part on EMEA governance)²⁶, together with specific cost monitoring tools:

- ▶ Activity based budgeting (ABB);
- ▶ The electronic EMEA time management system "ActiTrak" to collect data for activities according to source of revenue;
- ▶ A scoreboard system for monitoring the implementation of their work programme.

The EMEA has set up a monitoring system consisting of some performance indicators covering all its main activities. The follow-up on these indicators is published in different reports (activity reports, annual reports, work programs). It allows consistent monitoring of the activity of each EMEA unit.

With regards to the cost accounting system, the work program 2000-2001 emphasised already the necessity to focus the attention on costs evaluation.

This mission is mainly carried out by the personnel and budget sector, and supported by ActiTrak. In particular, this tracking system supports the monitoring of the activity based budgets and contributes to a better allocation of resources.

EMEA evaluation activities are efficiently managed

In order to assess whether EMEA resource allocation is consistent with its activities, we calculated rates comparing the volume of the analysed activity to the dedicated costs. The trend of these rates over the years has been analysed. A significant increase would suggest a loss in efficiency for certain type of activities, thus identifying potential room for improvement.

The resources dedicated to evaluations have increased following the increase of applications demonstrating a stable efficiency on the activities performed on initial applications

From an external perspective, we may assume that the assessment process performed by two independent Rapporteur teams along with the Peer review does not allow an efficient allocation of resources, because some activities are potentially duplicated.

²⁶ EMEA, The European Medicines Agency Road Map to 2010: Preparing the Ground for the Future, March 2005

However, as proved in the answer to the first evaluation question, a fair and highly valued scientific evaluation requires these multi level assessments and review steps.

On Figure 33, we compared the total costs dedicated to evaluation activities, which consists of the sum of EMEA Secretariat internal costs and the commitments to NCAs.²⁷

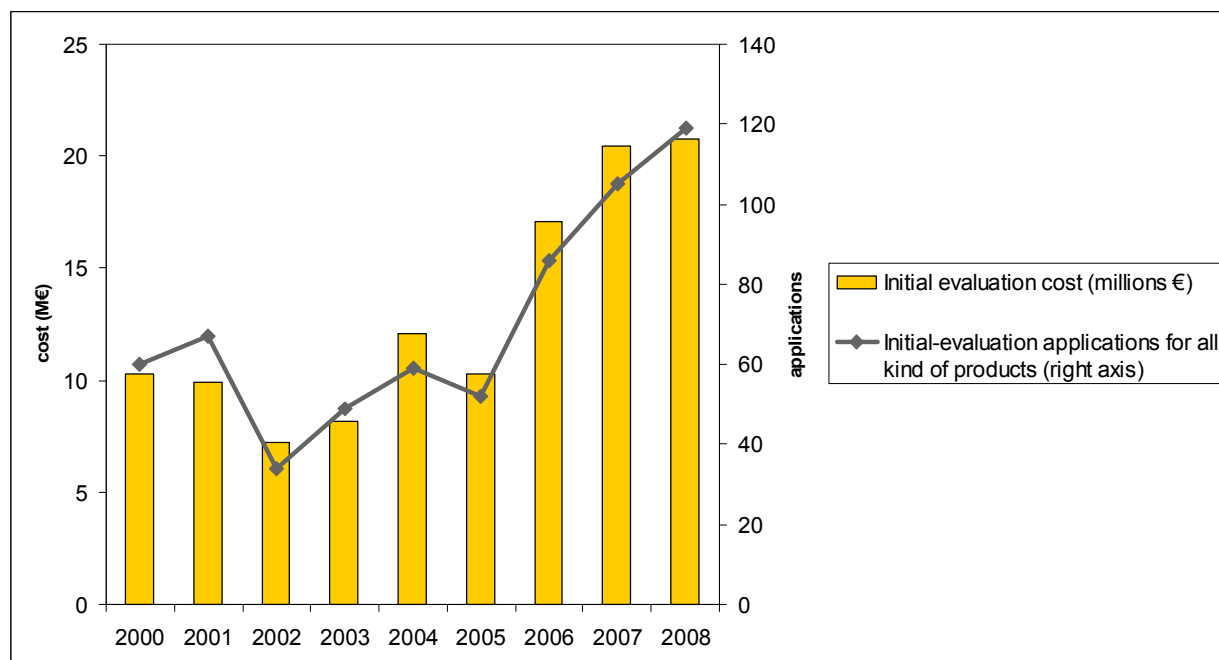


Figure 33: EMEA initial evaluation costs versus total applications for human and veterinary medicines

Source: EMEA Activity Based Budget, EMEA annual reports

NB: there is no assurance that the costs incurred in a particular year are related to the evaluation of an application conducted the same year because costs are monitored on a cash basis while an accrual method is used to count the application. Nevertheless, it allows making some preliminary analysis.

Looking into the details to the Figure 33, it appears that the ratio cost per application may improve from one year to another. No clear explanation has been identified for this because the causal link between an application and the total costs incurred depends on too many factors: e.g. regulatory complexity, types of molecules, scientific involvement of EMEA Secretariat, etc.

Globally, Figure 33 shows a stable efficiency on the activities performed on initial applications. Indeed, costs dedicated to evaluation activities have doubled over the past 8 years, thus following the increase in the number of applications (see Figure 34).

	Average 2000-2005	Average 2005-2008	Increase
Initial-evaluation applications for all kind of products	54	103	+91%
Initial evaluation cost (millions €)	10	19	+90%

²⁷ EMEA, Activity Based Budget, 2000 to 2008

Figure 34: Average EMEA initial evaluation costs versus average total applications for human and veterinary medicines

Source: EMEA Activity Based Budget, EMEA annual reports

The EMEA Secretariat as well as the EMEA support activities have gained in efficiency since 2000

A 150% increase of its staff is legitimate with regard to the increase of its activities

It is noticeable to say that the EMEA Secretariat demonstrates a increase in the growth of its staff that is in line with the increase of its activities (see Figure 35 where the staff considered are the temporary agents, and where the fees collected have been selected as the most representative indicator of the activity). EMEA staff has increased by 150% over the period 2000-2008, while the fee revenue has increased by 220% (in addition, some activities are not linked to fees: orphan-designation, paediatric and referral-related activities, etc).

The Secretariat staff is composed of temporary agents recruited through open selection procedures. They are offered five-years renewable contracts. Contract agents are also used for short term periods and represent a significant workforce in the agency (57 in 2007, versus 423 temporary agents).

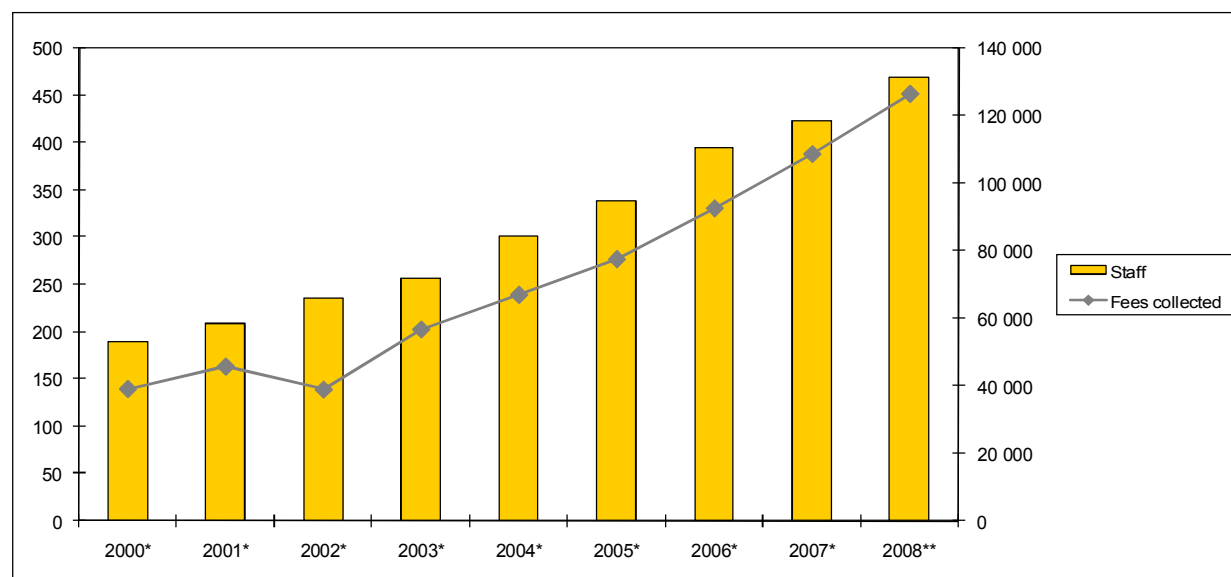


Figure 35: Evolution of staff number versus fees collected

Source:

Staff bars: EMEA Establishment plan (*occupied as per end of year - **authorised as per the establishment plan 2009)

Fees curve: EMEA annual budgets (*Budget/Appropriation of year Y as of end of year Y - **Budget/Appropriation 2008 as of 17 November 2008)

Some key activities have gained in efficiency however scope for improvement still exists

Although EMEA efficiency is globally recognised by the stakeholders, two areas of improvement were mentioned during the interviews: the pharmacovigilance and the herbal medicinal products activities. The

following cost-effective analysis of the main EMEA activities will challenge this feedback on a factual basis.

Pharmacovigilance activities

Pharmacovigilance activities are the most resource-consuming activities over the period 2000-2008 (on average about 13% of the total costs).²⁸

The output analysis is limited since the scope and responsibilities of the pharmacovigilance activities are more complex compared to the initial application evaluations.

The most relevant outputs of pharmacovigilance and maintenance activities would be:

- The number of Adverse Drug Reaction (ADR) (EU and non EU) managed by EMEA: however, one should keep in mind that the number of ADRs sent to EMEA is mostly independent of EMEA;
- The Periodic Safety Update Report (PSUR) managed by EMEA: here again, the number of PSURs communicated to EMEA is directly correlated with the number of medicines on the market and the date of their marketing authorisation, as there are rules as to the frequency of PSUR depending on the time a drug has been launched on the market (see section 5.3.4).

The following graph (Figure 36) compares the costs related to EMEA pharmacovigilance and maintenance activities, as identified by the EMEA, with the above described types of output. Between 2000 and 2008, costs have been multiplied by 3.7 whereas ADRs number has been multiplied by 7.5 and the PSURs number by 1.9. From this, it can be concluded that the EMEA has gained in efficiency. The management of PSUR is more time-consuming all the more that they require more and more follow-up.

However, we have to keep in mind that pharmacovigilance activities do not aim at increasing the number of adverse drug reactions (even if improved pharmacovigilance systems leads to more reactions reports): on the contrary, a decrease of reported reactions may also be interpreted as a positive impact of effective pharmacovigilance systems. The analysis of the cost-effectiveness of such activity therefore needs to be considered very carefully.

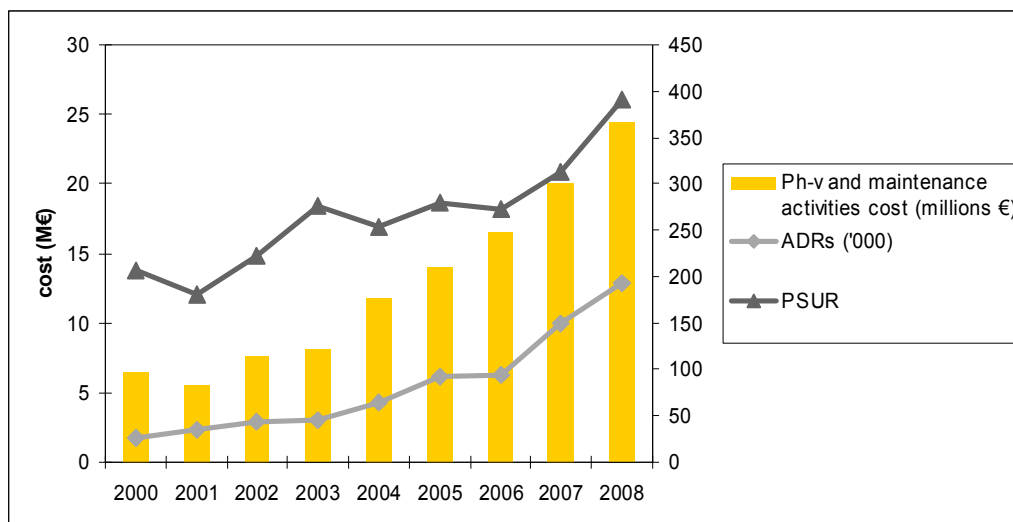


Figure 36: EMEA pharmacovigilance costs versus total number of ADR and PSUR

Source: EMEA Activity Based Budget, EMEA annual reports

²⁸ EMEA, Activity Based Budgets, 2000-2008

The concerns related to pharmacovigilance activities will be discussed in more details in paragraph 4.3.5. In terms of efficiency, there is a need to streamline the pharmacovigilance activities in the EU to avoid any duplicate submissions and ensure the quality of submitted data. The EudraVigilance system is set up to avoid this duplication.

Scientific Advice (including protocol assistance) activities

EMA activities related to scientific advices (SA) and protocol assistance (PA) also showed an important increase between 2000 and 2008. The following graph (Figure 37) compares the evolution of SA and PA finalised to the evolution of costs for SA and PA, reported by the EMA cost-tracking system. Both are increasing quite similarly, however a slight improvement in cost-efficiency can be noticed.

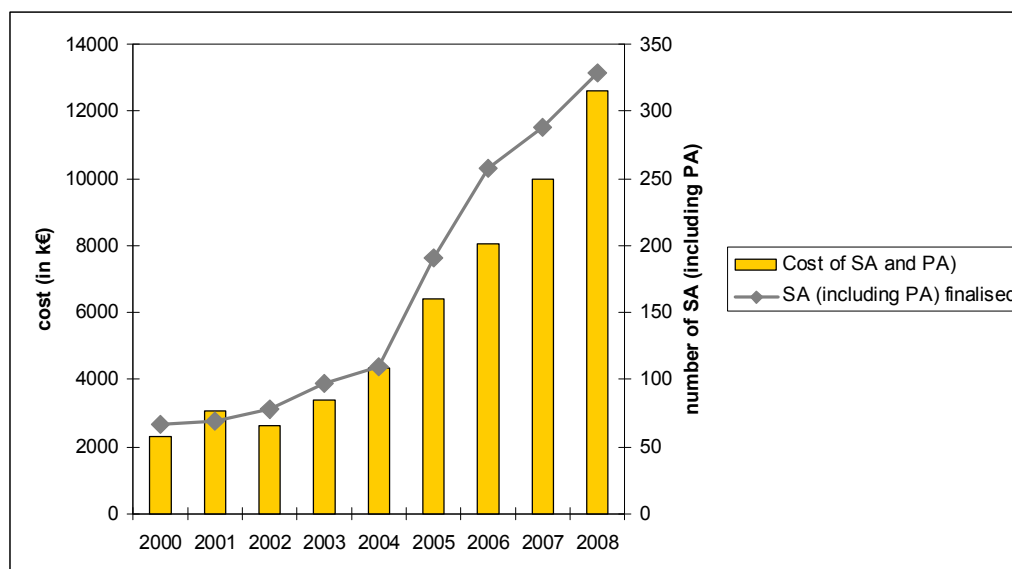


Figure 37: EMA scientific advice costs versus total number of scientific advices finalised

Source: EMA Activity Based Budget (cost have been taken excluded of support services), EMA annual reports

The focus on cost efficiency allows establishing a rough estimation of cost per SA (including protocol assistance). It is however important to note that there are different types of Scientific Advice and Protocol Advice provided by the EMA and that our measure does not discriminate between them, which may explain the high variability in costs observed. Average cost per SA/PA in a given year ranges between 31 k€ and 44 k€ between 2002 and 2008, with significant peaks in 2001 and 2004. As shown below in Figure 38, there is a slightly decreasing trend over the years, however this should be considered carefully because of the variability of the costs. It may however be considered as a positive sign for the efficiency, taking into consideration the dramatic increase in the number of scientific advices (almost 5 times increase over 2000-2008). One would have expected an increase in costs to manage this increase.

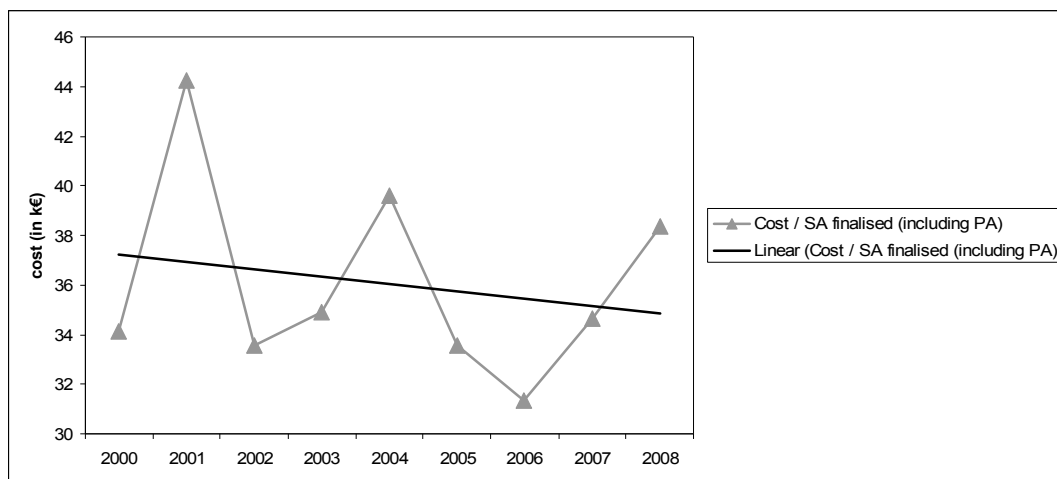


Figure 38: Evolution of cost per SA (including PA) finalised

Source: EMEA Activity Based Budget (cost have been taken excluded of support services), EMEA annual reports

Herbal medicinal products

EMEA activities related to herbal medicinal products have in some cases been mentioned as an area of investigation for further improvements.

More specifically, although EMEA activities regarding herbal medicinal products have not been identified as a bottleneck, the costs allocated to herbal products are relatively significant: between 1,4M€ in 2006 and 1,7M€ in 2008 (around 1% of EMEA budget), while between 2,3M€ and 2,5M€ (1,4% of EMEA budget) was spent on orphan designation procedures in the same period.²⁹ This observation should be moderated by the importance of tasks performed by HMPC. HMPC has to ensure that herbal medicinal products in the market are checked for efficacy and safety through the development of product monographs and list entries. These medicines, mostly used as traditional remedies, are very numerous and may not be as safe as commonly perceived. Moreover, because these are mostly traditional medicines, the efficacy of some herbal products is difficult to assess because of the limited clinical trials that have been completed for them.

The establishment of the HMPC is supported by the request of the European Parliament to benefit to the European public health, and is therefore answering the need to coordinate the herbal products evaluation. Its costs are therefore not the main point of concern.

Orphan applications

The figures below are further indicating an increase in efficiency in relation to the resources concerned:

	2001	2002	2003	2004	2005	2006	Increase
Orphan designation applications	83	80	87	108	118	104	25%
Administrators to perform this activity	4	4	4	4	4	4	0%

Figure 39: Evolution of orphan designation applications versus dedicated staff

Source: EMEA staff policy plan (budget exercise 2008)

²⁹ EMEA, Activity Based Budget, 2000-2008

Post authorisation activities

	2004	2005	2006	Increase
Post-authorisation activities	304	364	557	83%
Number of established posts in Specialised Groups	23	25	25	9%

Figure 40: Evolution of post-authorisation activities versus dedicated staff

Source: EMEA staff policy plan (budget exercise 2008)

The departments of the EMEA Secretariat expressed their concerns about the difficulty they perceived to hire new staff and the length of the budgetary process to get additional positions. Furthermore is the EMEA Secretariat encountering difficulties in hiring highly qualified experts in accordance with its enlarged competences (see the part about the effectiveness of the EMEA Secretariat). Targeted profiles without any conflict of interest belong mostly to public services and are often reluctant to leave their career as civil servant (meaning losing their acquired rights).

EMEA support activities have gained in efficiency with a decrease in the weight of administrative costs over the period 2000-2008

Support services costs (e.g. executive support, personnel management, budget, accounting and infrastructure service) have increased as expected following the increase in the EMEA structure and the enlargement of scope. However, their weight in the total costs has significantly decreased over the period 2000-2008. In addition, the number of staff members dedicated to support services has not changed between 2005 and 2007 while the corresponding workload has significantly increased (more staff to manage, more operational and financial transactions, etc).³⁰

It is difficult to find a comparable organisation to benchmark these costs to. However, it appears that the dedication of about 15% of the resources to administrative tasks (average between 2000 and 2008) can be considered as reasonable. This ratio is even more remarkable considering that the EU enlargement and the revision of the pharmaceutical legislation have significantly increased the complexity of EMEA operations.

³⁰ EMEA staff policy plan, 2008

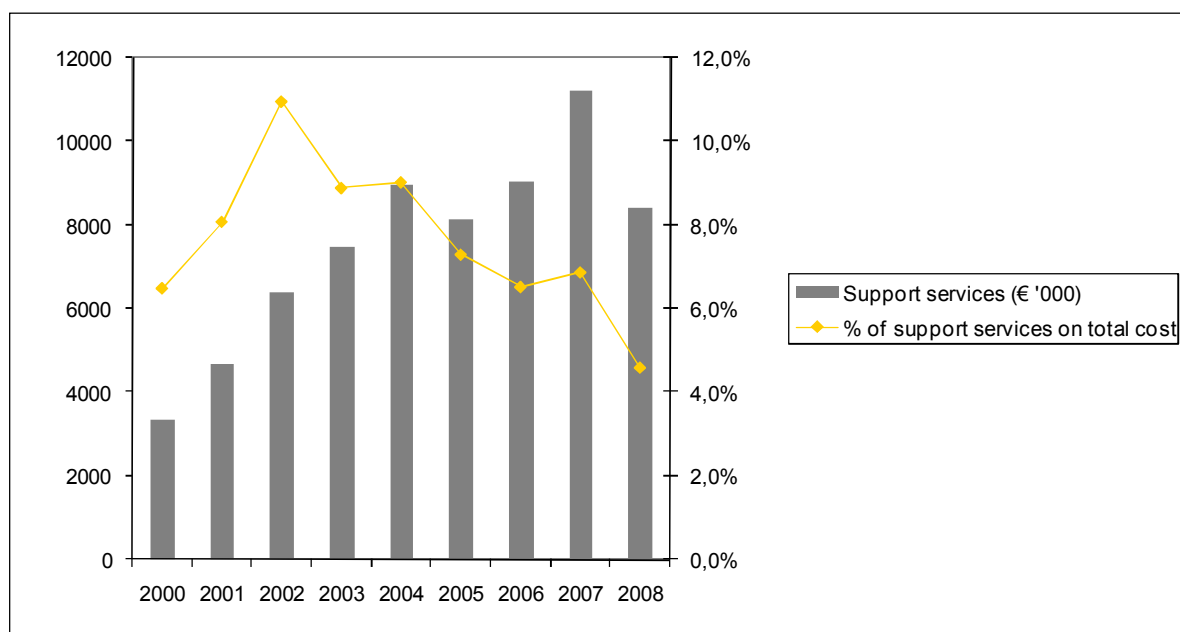


Figure 41: Support Services (executive support, personnel management, budget, accounting and infrastructure service) budgets and corresponding percentage of total expenses 2000 – 2008

Source: EMEA Activity Based Budgets 2000-2008

EMEA financial management is focusing on specific area for cost-optimisation

Measures on fixed costs may allow decreasing costs of EMEA outputs

Figure 42 shows the part of fixed costs in the total budget of the Agency. As represented by the trend line, this percentage has slightly increased over the years.

Fixed costs are defined in contrast to 'operating expenditures' that are clearly linked with EMEA activity. For practical purposes, the budget line 'Buildings, Equipment and miscellaneous operating expenditure' is considered as giving a fair representation of the fixed costs supported by the EMEA. This budget heading includes following types of expenditure:

- ▶ Investments in immovable property, renting of buildings and associated costs: rent, insurance, etc;
- ▶ Expenditure on data processing: maintenance of computer networks and equipment (purchase, hire and maintenance of hardware and software);
- ▶ Movable property and associated costs: technical equipment and installations, furniture, vehicles, documentation and library expenditure;
- ▶ Current administrative expenditure: stationery and office supplies, financial charges, legal expenses, publications, etc;
- ▶ Postal charges and communications;

► Expenditure on formal and other meetings.³¹

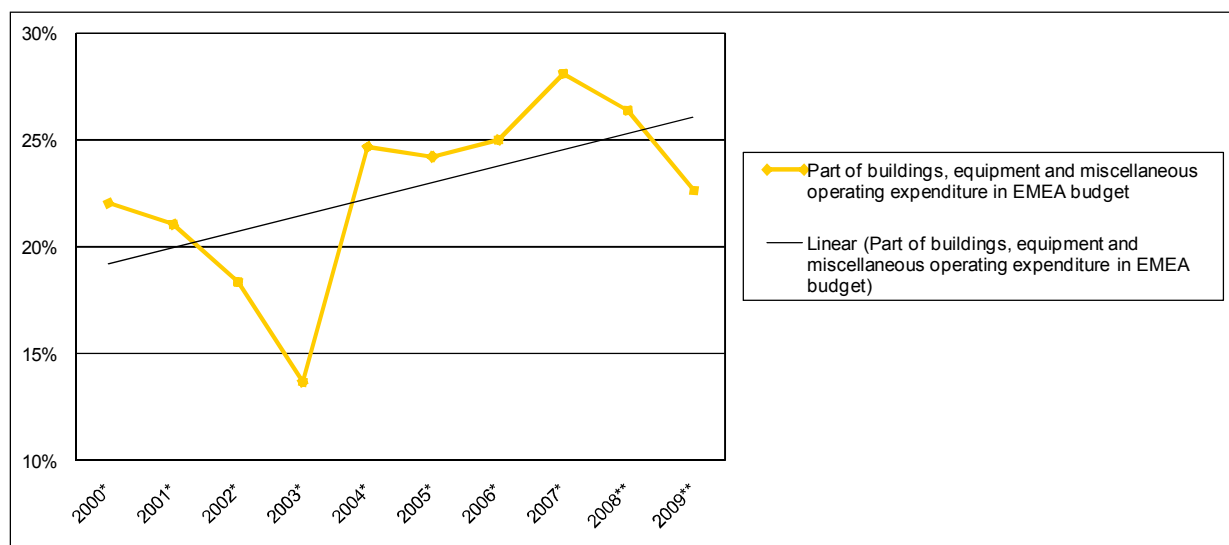


Figure 42: Part of buildings, equipment and miscellaneous operating expenditures in EMEA budget

Source: EMEA annual budgets (* Outturn year Y as per Final Accounts - ** Budget appropriation as of year-end)

The increasing weight of fixed costs is further highlighted by Figure 43. It stresses an higher raise in fixed costs compared to the trends for staff and applications.

	2000-2008 increase
Buildings, Equipment and miscellaneous operating expenditure	+304%
Initial-evaluation applications for all kind of products	+98%
Number of staff	+148%

Figure 43: Comparison of the raise in fixed costs, staff expenses and initial evaluation applications between 2000 and 2008

Source: EMEA annual budgets (2006, 2007 and 2008), EMEA annual reports (2006, 2007 and 2008)

Most important increase over the period 2000-2008 concerned data processing expenditure which includes expenditure for the EU telematics systems. While this type of expenditure represented 4% of EMEA budget in 2000 (2,4M€ over 54,3M€), they count for 11% of total expenses in 2009 (22M€ over 194,4M€). Since 2007, these costs are higher than immovable investments, renting of building and

³¹ This definition of fixed costs is rather broad as used in management accounting. Some costs like posts and telecommunications charges could be considered as variable. However such costs are more charges of support services and not directly linked with EMEA core activities (e.g. telecommunications yearly subscription costs remain whatever the level of activity is).

associated costs. Investments in complex and pan-European IT infrastructures had therefore a significant impact on EMEA budget: development of telematics has been outsourced to external providers which represented important costs for the EMEA. While EMEA IT department still plan to outsource development works, maintenance costs are expected to be internalised through recruitment of dedicated internal resources (a decrease of data processing expenditure is already to be noticed in 2009)

Second highest type of fixed costs is 'Investments in immovable property, renting of buildings and associated costs'. These costs also strongly increased over the years however their part in total budget is lower in 2009 (9%) than in 2000 (14%).

As a comparison, the FDA, rental payments and costs (budgetary lines: rental payments to GSA, operation & maintenance of facilities and Land & Structure) are representing between 10% and 11.5% of the total expenses in the last three years.³² However, the US agency is also managing a USA-wide inventory of leased and owned real property assets that includes a substantial amount of laboratory facilities.

By comparison with another European regulatory agency, the Office of Harmonisation for the Internal Market (OHIM) based in Alicante-Spain, the part of buildings and associated costs is even smaller: buildings, equipment and miscellaneous operating expenditure represents 5.3% of total expenses in 2006, 2.2% in 2007 and 2.7% in 2008. The adopted OHIM budget for 2009 estimates 4.1% of expenses for this budget heading.³³

While EMEA location costs may be considered as quite high, some specificities of the Agency balance this statement:

- ▶ The space needed for the arrangement of meetings has increased with the establishment of new committees and working groups. Such space is considered necessary to accommodate EMEA evaluation activities, which are its core business. Unfortunately, spaces for meetings are most of the time "unproductive", i.e. unused (only 40% of the buildings are currently occupied by full time employees);
- ▶ The rent level in London (4000£ year per m²) is the highest in Europe.

On the whole, it remains difficult to judge the level of EMEA fixed costs, given the political decision to set up the Secretariat in London on the one hand and the specific features of this network's organisation like telematics on the other hand. Current level of fixed costs may be considered as quite high. However, the impact of telematics on EMEA fixed costs is expected to decrease over the next years, and progressively reach a level similar to comparable organisations.

The development of long-distance collaboration tools should contribute to decreasing the meetings expenses

According to the Activity Based Budgets, between 10.5M€ in 2000 and 16.1M€ in 2008 has been yearly allocated to the management of the CHMP, CVMP and Working Parties meetings.

The weight of the costs for the organisation of committees and working parties meetings (reimbursement to delegates and management for travel and accommodations expenses, plus organisation expenditures) decreased as percentage of the total EMEA budget (see Figure 44). According to internal stakeholders, it appears to be still very useful to pursue the network setting. More extensive use of

³² FDA, Program Level Budget, 2006, 2007 and 2008

³³ OHIM, Budget for the Financial Year, November 2007

information and communication technologies as alternatives to physical meetings and the implementation of the Meeting Document and Management Systems contribute to further reduction of such costs. More than 600 meetings are organised yearly and the systems support the electronic distribution and use of documents as well as organisation of travels booking: each meeting required the production of around 1 ton of paper until these systems were implemented, not even considering the savings in travel expenses. Many stakeholders have recommended further pursuing efforts promoting virtual connections and meetings for the EMEA network.

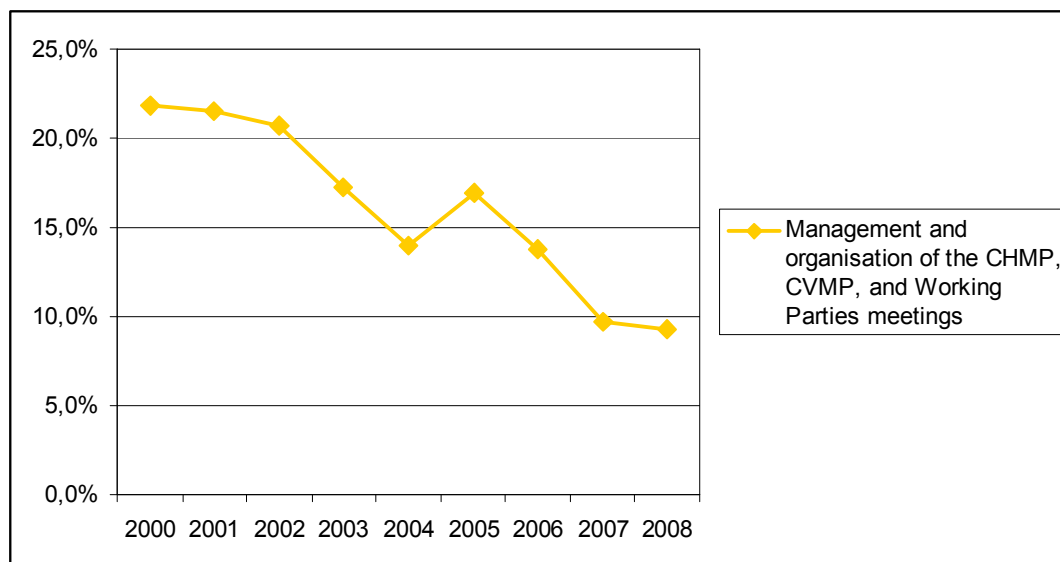


Figure 44: Management and meetings costs weight in the total EMEA costs

Source: EMEA Activity Based Budget 2000-2008

The EMEA is currently increasing its technical capabilities to increase the use of teleconference, which would definitely decrease the meetings costs. Moreover, it could increase the contribution of some experts that are sometimes reluctant to undertake too much travel. In order to benefit properly from the collaborative tools, the agenda of the meetings will need to be adapted, i.e. preferring rather short meetings.

NCA must also be equipped by such tools, which is not systematically the case today. NCAs using teleconference tools underline the better quality of Vitero teleconference system with regards to other systems (see the part on the support provided by EMEA IT systems to NCAs).

The EMEA promote paperless authorisation processes to reduce the cost of data exchanges

The EMEA promotes paperless workflows not only internally, but also in the exchanges with the industry. A strong cooperation with EFPIA has been set up for the development of an electronic submission tool, e-CTD. This project aims at implementing the electronic format for the marketing authorisation application developed by the ICH. The end of 2009 was the target date for adopting an electronic format for centralised procedures applications.

The EFPIA express very positive feedback on EMEA inputs, such as:

- Technical specification;

- Clear plan of action.³⁴

The centralised procedure under EMEA responsibility is here again considered as a good practice that should be used as a benchmark for other types of procedure. The EMEA and the industry are willing to continue their collaboration towards a fully electronic centralised procedure. Such paperless systems produce savings for both parties and support the implementation of a seamless process.

³⁴ Dr G. Williams (IFAH), e-CTD/Nees impact on the Centralised Procedure, February 2009

The evolution of EMEA financial resources is consistent with its activities

Industry fees represent two thirds of the EMEA annual budget

As per Regulation No 726/2004, the Agency's revenue shall consist of a contribution from the European Commission plus fees paid by the industries for the services rendered by the EMEA: it represents two thirds of the EMEA budget in average over the 2000-2008 period.

EMEA resources have continuously increased (except in 2002) from 2000 to 2008 with an average rate of 17%.

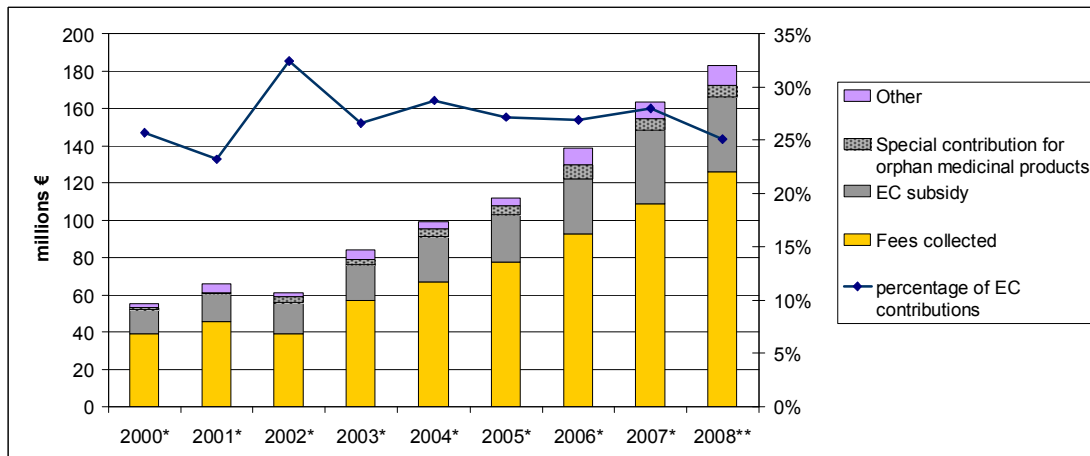


Figure 45: Budget evolution per type of contribution from 2000 to 2008

Source: EMEA annual budgets (*Budget/Appropriation of year Y as of end of year Y - **Budget/Appropriation 2008 as of 17 November 2008)

On average over the period 2000-2008, about 66% of the budget is made by the fees paid by the industry. About 94% of the fees are paid by human medicines pharmaceutical companies. At the FDA, the fees constitute not more than 25% of the overall budget, but FDA mandate is more broad (e.g. food safety) and impacts consequently its budget structure. Type II variations, initial applications and annual fees constitute more than 80% of the fees collected for human products (see Figure 46).

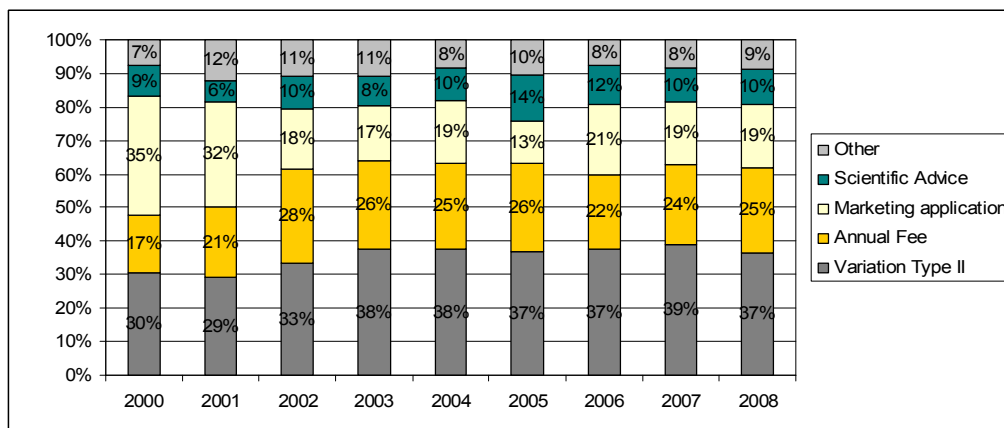


Figure 46: Fee income per type of activity for human products

Source: Fee income by type of activity 2000-2008

As a consequence, the EMEA resources are mostly driven by the pharmaceutical industry activities

As the fees represent the main contribution to the EMEA budget, the pharmaceutical industry activity, and mainly the number initial application and variations submitted, concerns the EMEA resources.

A strong correlation is observed (see Figure 45) between the evolution of the initial applications submitted and the budget. A similar observation can be made for the evolution of type II variations. Globally, it is therefore assumed that the **pharmaceutical industries dynamism has had a greater impact on the EMEA budget** than the regulation changes or some contextual changes like the EU enlargement.

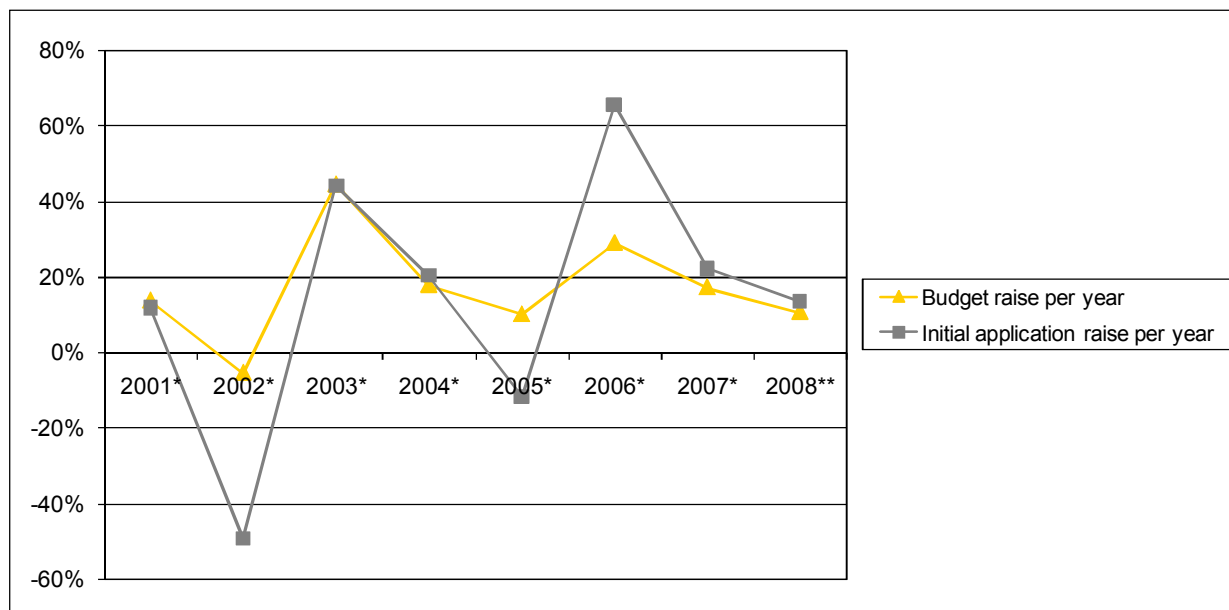


Figure 47: evolution of the budget versus number of initial applications for all kind of products (human and vet)

Source: EMEA annual reports, EMEA annual budgets (* Outturn year Y as per Final Accounts, ** Budget appropriation as of year-end)

A full fee for marketing authorisation applications for human use products amounts 251 600 euros while a similar application (i.e. requiring clinical data) at the FDA costs 1 405 000 dollars (about 955 400 euros). This topic will be further discussed in section 5.4.1.

EMEA budget is built to cover its needs

The budgetary process together with a tight follow up of its expenses allows the EMEA budget to cover the needs

The Agency prepares the budget and the Management Board adopts the final document. The Secretariat is drafting its estimation in a comprehensively documented process involving all stakeholders concerned. The budget estimate is built based on an in depth analysis of the pipeline of the pharmaceutical and biotech industries. The objective is to estimate the expected resources for the evaluation activities, EMEA “core business”.

On the basis of this estimation, European institutions (the European Commission and the European Parliament) determine during the budgetary programming process the amount of subsidies coming from:

- A balancing contribution from the EU general budget to support the EMEA activities;

- A specific subsidy to compensate the Agency for fee exemptions: orphan products in particular but also special contributions dedicated to telematics projects.

The EMEA budget consumption monitoring is processed in such a way that it covers the costs of the EMEA. EC contribution may be used to compensate the variation in industry fees. Figure 48 shows that the significant 2002 decrease in industry fees has been compensated by an increase in EC subsidy. In recent years, fee revenues have been higher than expected, thus allowing to build a reserve that can be used as earmarked revenue in case of fee income fluctuation in following years.

This compensation is a guarantee for the various stakeholders (and EU citizens in particular) that the EMEA will achieve its objectives without being potentially affected by external fees fluctuation and therefore is able to contribute to the EMEA resources sustainability.

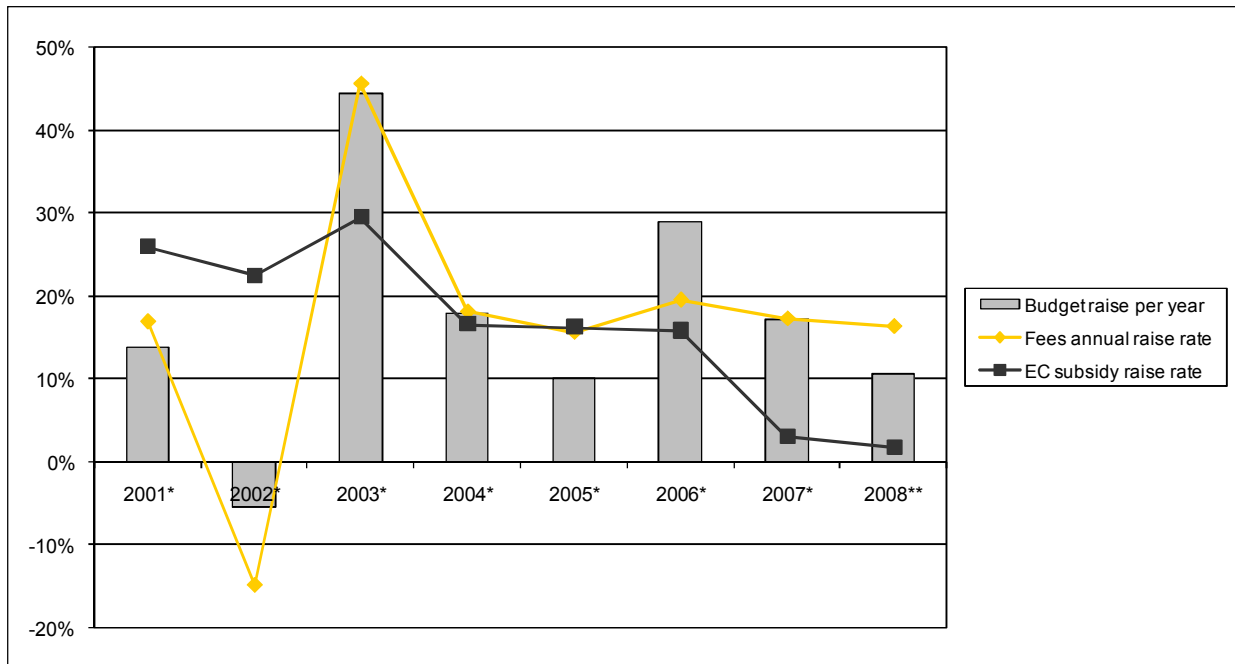


Figure 48: Annual raise of the EMEA budget, industry fees and EC subsidies over the 2001-2008 period

Source: EMEA annual reports, EMEA annual budgets (* Outturn year Y as per Final Accounts, ** Budget appropriation as of year-end)

However some clarification and flexibility in the financing model could be introduced

The EMEA Secretariat is requesting more flexibility in its use of the budget:

- ▶ As a European agency, the EMEA should respect the principle of annuality (principle to which expenditure and revenue are authorised for one year). However, a reserve facility has been awarded in case of fluctuation of the Agency's fee revenues in future years. While this reserve is used with particular care (through a dedicated budgetary procedure), the EMEA Secretariat would appreciate to extend this multiannual flexibility to the funding of specific projects. It is particularly appropriate for EU Telematics projects where the nature of the projects makes it difficult to strictly comply with the annual budget principle.
- ▶ The EMEA is considering using the fees to finance other services provided to companies (like databases from which companies also benefit) than only the related operational tasks. However there are some regulatory limits to cross subsidisation between fee-related and non-fee related activities. The discussion of cross subsidy is raising several issues related to accounting practices. There is certainly a need for more clarity and transparency on those issues in the regulation. Indeed, the cost

coverage of some activities (non fee paid activities in particular) remains unclear to most EMEA stakeholders (see later).

NCA are compensated for some activities only

One third of the EMEA budget has constantly been dedicated to NCAs

Between 2000 and 2008, the part of the EMEA total expenditure dedicated to NCAs remains quite stable (32% in average).

	2000*	2001*	2002*	2003*	2004*	2005*	2006*	2007*	2008**
EMEA total expenditure dedicated to NCAs	32%	31%	29%	32%	32%	32%	36%	33%	33%

Source: EMEA annual budgets (*Outturn of year Y as per Final Accounts **Budget/Appropriation as of 17 November 2008 incl. AB 02-2008), EMEA statistics “Commitment to NCAs by fee type”

These costs dedicated to NCA are mainly related to marketing authorisation and post-authorisation activities (see Figure 49).

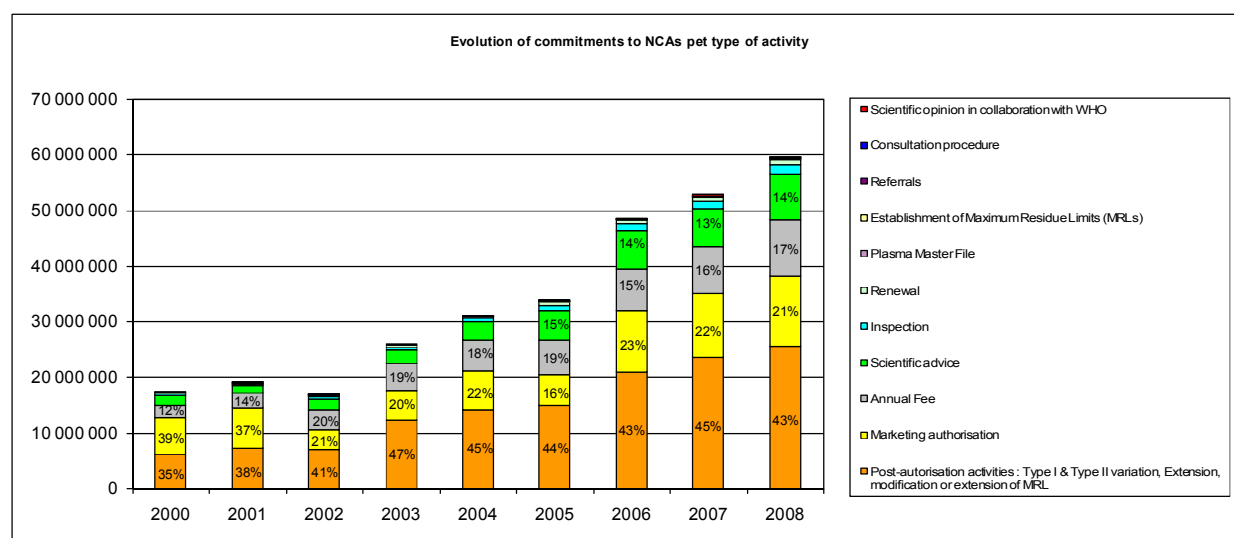


Figure 49: Evolution of commitments to NCAs per activity

Source: EMEA statistics “Commitment to NCAs by fee type”

NCAs contribution to the EMEA is compensated by several channels:

1. In accordance with Article 62(2) of Regulation (EC) No 726/2004 and Article 11(1) of Council Regulation (EC) No 297/95, the different NCAs subcontracted by the EMEA for evaluation services received a fixed percentage of the fees to which the services relate.

2. In addition to the fees related to performed procedures, an annual maintenance fee is charged to the Marketing Holder Applicant in respect of post-authorisation monitoring activities required by the legislation. The distribution of this annual fee is the following:

- 30 percent for EMEA pharmacovigilance and inspection staff costs
- 30 percent to be divided between Rapporteurs and Co-Rapporteurs where applicable for scientific evaluation services provided at the request of the EMEA (e.g. annual product reports and specific reporting for pharmacovigilance and safety reports).

- 30 percent to be attributed to special activities to be determined by the Management Board, in consultation with EMEA scientific committees.
- (up to) 10 percent under the EDQM-EMEA scientific agreement and programme for sampling and testing of centralised products.

The scope of these “special activities” is indicated in the Rules for the implementation of Regulation (EC) No 297/95 as amended on fees payable to the European Medicines Agency and other measures” (EMEA/MB/170391/2009/Rev.1/Adopted). Fee exemptions are part of this scope, but compensation process is not clear and does not appear to be sufficient (see below).

3. Travel and accommodation expenses are fully reimbursed; daily subsistence allowance is provided.

The NCAs compensation process of “non fee related services” lacks of transparency

Some evaluation works performed by EMEA are non payable by the industry, or may benefit from fee exemptions. Orphan medicinal product designations under Article 7(2) of Regulation (EC) No 141/2000 are compensated by EU subsidy. However, other non-fee related services are partially or poorly compensated, especially:

- ▶ Medical products for paediatric use;
- ▶ Referrals under Articles 29, 30, 31 and 35 of Directive 2001/83/EC (human medicines) and Articles 33, 34, 35 and 39 of Directive 2001/82/EC (veterinary medicines): work on the referrals is not compensated, unless the referral was initiated by a company;
- ▶ SMEs are also eligible for fee reductions for scientific services (including scientific advice , inspections and evaluation of advanced therapy medicinal products), and fee exemptions for certain administrative services.

5.2.2. NCAs network involvement

NCAs are dedicating an increasing part of their activity to the EMEA, however this is limited by a stringent lack of resources

From an external point of view, the EMEA benefits from a tremendous advantage with its NCAs network compared to other regulatory agencies in the world. The Japanese Pharmaceuticals and Medical Devices Agency (PMDA) face a lack of resources in specific areas and when looking at the EMEA, it considers the NCAs network as a great opportunity to find relevant experts.

However, such network also implies very heterogeneous types of involvement and levels of actors.

Several types of involvement of NCAs in the EMEA have be considered

NCAs involvement must be considered by distinguishing:

- ▶ **Common involvement:** all NCAs are participating in Committees meetings. Each of them is required to send at least one member to CHMP, one to CVMP, sometimes the same representative or another one to COMP, PDCO and HMPC committees.
- ▶ **Additional involvement through different types of activities:**
 - Being chair of the Committees (requires an additional workload in order to prepare the meetings and lead the opinion making process);
 - Taking Rapporteurship/ Co-Rapporteurship or being appointed as a reviewer is seen as the heaviest involvement for a Member State ;
 - Participating in working parties, scientific advisory groups or other expert groups ;
 - Providing scientific advice;
 - Contributing to assessments by reviewing the file presented by the rapporteur / co rapporteur at committees.

All NCAs have reported a clear increase in their overall workload related to EMEA activities

97% of NCAs confirm an increase of the overall workload related to the EMEA activities. The most quoted reason is the consequence of the recent legislation (see Figure 50): NCAs report a higher level of input is required for in the new committees, COMP and PDCO, compared to the two central committees CHMP and CVMP (question 20.2).

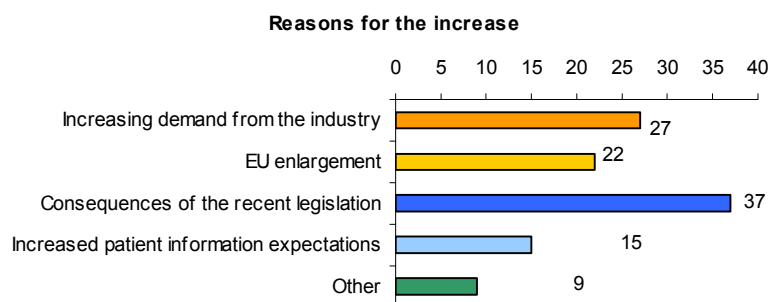


Figure 50: Question 12.2. In your opinion, what are the reasons for this increase?

Source: Ernst & Young NCA questionnaire, June 2009

NCA involvement strongly depends on their capacity, financing model and mandate

NCA present very different models in terms of status, link with their administration, mandate and funding system.

Three main types of status have been identified (see Figure 51): nearly 50% of the agencies are depending on another institution.

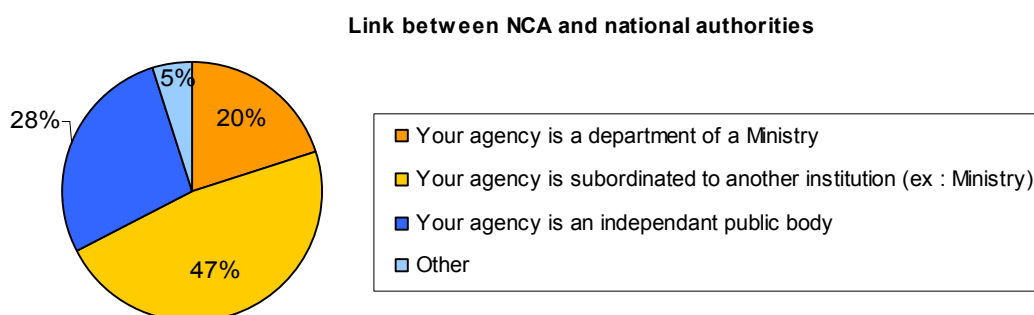


Figure 51: Question 1.3. Link between the National authorities and your agency

Source: Ernst & Young NCA questionnaire, June 2009

These characteristics have an impact on:

- their resources: some agencies have a lot of experts in-house, while others are working more often with external experts;
- and their funding system: NCAs are more or less depending on fees for their revenues.

Besides these differentiations, **three types of agencies** can be distinguished with regards to their involvement in EMEA activities

- ▶ Large agencies are dedicating almost full-time experts to EMEA activities. These are leading agencies for Rapporteurships. On average, the key experts and heads of units of these large agencies are dedicating around 60% of their time to EMEA activities. The allocation of time of these experts has strongly evolved in the last few years: from 60% on national procedures and 40% on EMEA activities to the opposite.

- ▶ Medium Member States agencies are highly involved despite limited resources. This is in particular the case for the Dutch human agency that takes a lot of dossiers despite its smaller size. Sweden has also made a priority to be a major player at EMEA level, although being a relatively “small” country.
- ▶ Small agencies that cannot ensure a proper involvement in EMEA activities. They are therefore limiting their involvement to some expertises and therapeutic areas. Those NCAs pointed out that the time dedicated for the EMEA is often beyond ordinary national work time. The works comes
 - In addition to the traditional work at national level, considering that centralised procedures are still far less numerous than decentralised, mutual-recognition and national procedures, which require the same level of expertise;
 - without any additional financial resources except to one gained by the rapporteurships;
 - And without additional national resources.

Those agencies may send to London national representatives that have more time such as are retired employees.

As mentioned, although EMEA-related activities are covering a large spectrum, one main aspect can be easily quantified: the involvement in assessment dossier as Rapporteur or Co-Rapporteur. Our analysis will therefore focus more particularly on this aspect.

Thus NCAs involvement is unbalanced with seven Member States taking 75% of Rapporteurships and Co-Rapporteurships at the CHMP

On the human side, the reporting system for the allocation of Rapporteurships does not allow producing easily figures on past NCAs involvement as the follow up has been based on the name of Rapporteur (and not the Member State) until recently. However, the 2008 figures confirm that Rapporteurship and Co-Rapporteurship are mainly shared amongst only a few number Member States (see Figure 52): 7 Member States are taking 75% of Rapporteurships and Co-Rapporteurships: the United Kingdom, France, the Netherlands, Germany, Spain, Ireland and Portugal.

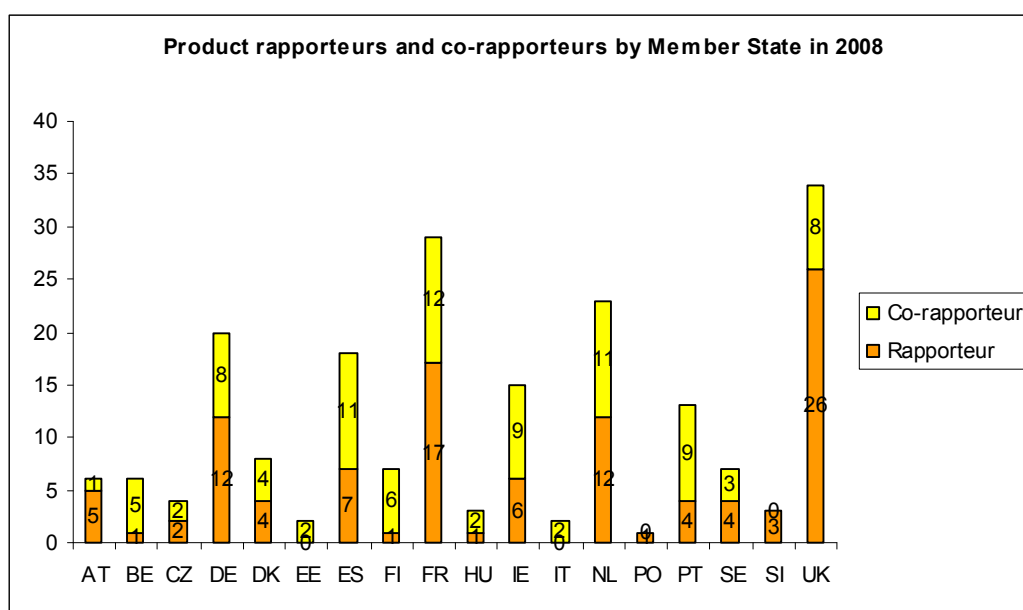


Figure 52: Member States' contribution as CHMP rapporteur/co-rapporteur for products in 2008

Source: EMEA statistics produced for the HMA resource group

This graph shows also that **new Member States are gaining confidence**. They took 12 dossiers in 2008, i.e. 6% of the total amount of Rapporteurships and Co-Rapporteurships:

- Czech Republic ; 2 Rapporteurships and 2 Co-Rapporteurships;
- Slovenia: 3 Rapporteurships;
- Hungary: 1 Rapporteurship and 2 Co-Rapporteurships;
- Estonia: 2 Co-rapporteurships.

With a broader perspective than Rapporteurship and Co-rapporteurship, it appears for instance that a larger number of Member States is involved in EMEA activities through their contribution to CHMP working parties (see Figure 53). While 18 Member States have been taking Rapporteurship or Co-rapporteurship for the CHMP in 2008, **23 Member States have been involved in CHMP working parties**.

NCA's are also dedicating a lot of resources to EMEA harmonisation activities such as guidelines or referrals, notably large agencies. National experts are aware of the importance of such activities. However, they prefer to dedicate time to assessment activities

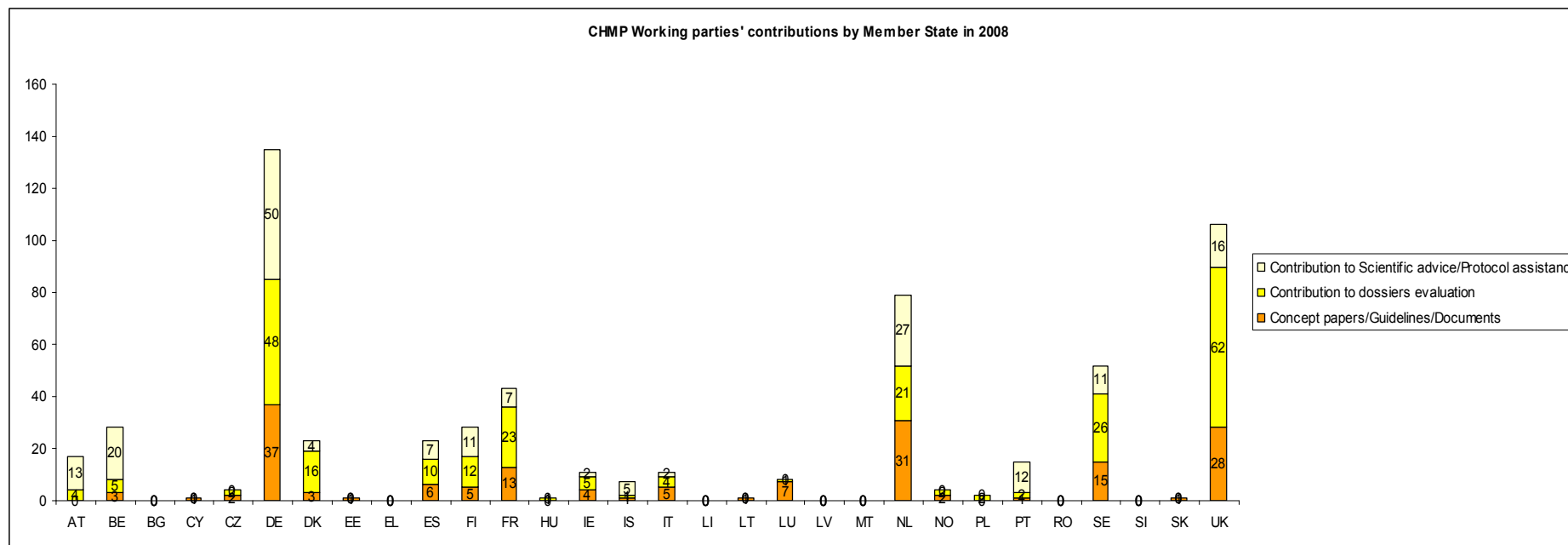


Figure 53: Member States' contribution as rapporteur/co-rapporteur for CHMP working parties' activities (Concept papers/Guidelines/Documents, contribution to dossiers evaluation or, contribution to Scientific advice/Protocol assistance) in 2008

Source: EMEA statistics produced for the HMA resource group

For the CVMP, the allocation of tasks and responsibilities is more balanced with two main contributors plus increased contributions from smaller Member States

On the veterinary side, figures regarding the evolution of the Rapporteurships allocation among NCAs are easier to produce and reveal interesting trends among NCAs.

The United Kingdom and Germany remain large contributors, however smaller Member States like Belgium or Denmark are taking more and more dossiers. For instance, Belgium has been the larger contributor in 2007 and 2008 with respectively 24 and 23 dossiers, mostly for variations type II. Even if variations and extensions dossiers are less demanding in terms of scientific workload, the total workload is more evenly distributed among NCAs.

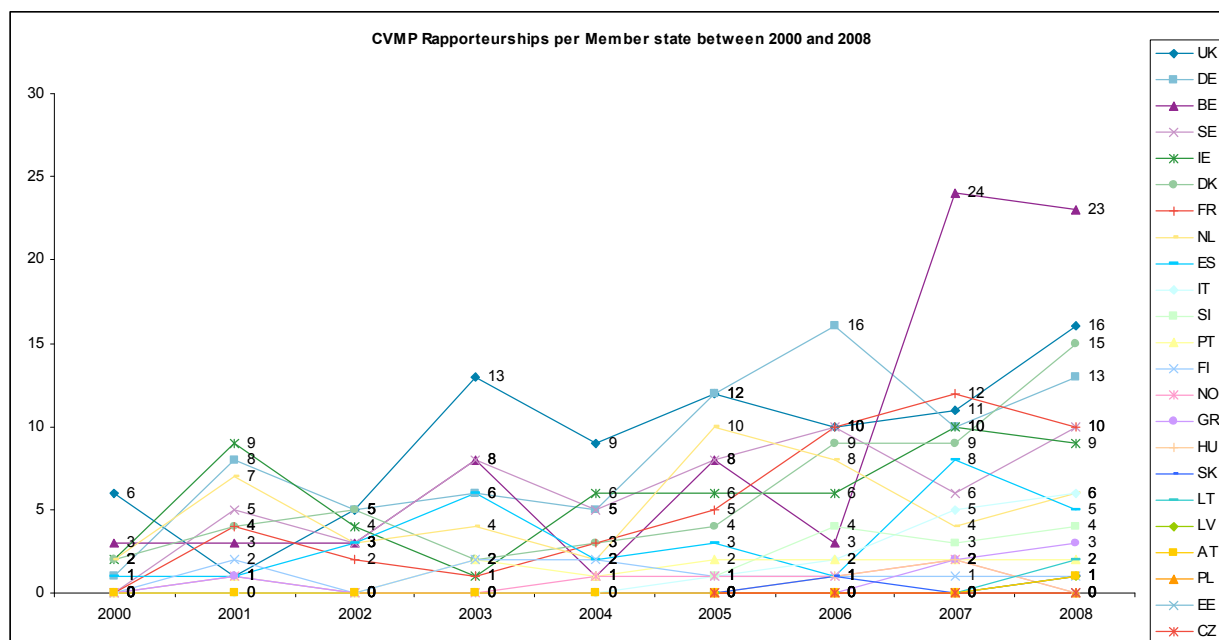


Figure 54: Member States' contribution as rapporteur/co-rapporteur for CVMP activities (as coordinator for Scientific Advice, Rapporteur/Co-rapporteur for Initial Evaluation, Rapporteur/Co-rapporteur for extensions, Rapporteur for variations Type II or Rapporteur/Co-rapporteur for referrals) from 2000 to 2008

Source: EMEA statistics

The new appointment procedure for Rapporteur and Co-Rapporteur, dated September 2009, taking into account the number of previously evaluated dossiers by the same Rapporteur (when deciding between equally qualified candidates), is aiming at a more balanced allocation of dossiers in terms of Member States.

Through the system, large contributors consider that most competent teams may not be awarded Rapporteurship and that therefore the assessments will lack of quality. However, peer-review and discussions at the meeting allow them to contribute (see the answer to the first evaluation question).

The evolution of the appointment procedure aims at improving and accelerating the mobilisation of the whole network in the long-term. Less active NCAs need such procedural incentive to gain expertise and confidence by taking Rapporteurship. Potential lack of expertise can still be compensated by other NCAs at different stages of the assessment process.

Reasons for contributing and non-contributing are diverse from the maintenance of a certain level of expertise to the facilitation of up-to-date knowledge on regulation and guidelines

For all types of NCAs, there are various reasons to accept a Rapporteurship (question 10.1), in decreasing order of importance:

- it allows to maintain a certain level of expertise (networking, exposure to other experts, exposure to scientific and regulatory evolutions...);
- it allows direct participation to the evolution of regulation and guidelines;
- local scientific expertise is available;
- it contributes to the agency's reputation;
- it facilitates up-to-date knowledge on the evolution of regulation and guidelines.

NCAs highlight the scientific interest and the ability to take directly part of the regulatory evolutions. **Associated fees are barely identified as the unique incentive** to apply for a dossier. While fees are a necessary component of Rapporteurships, they are not a sufficient motivating factor to appoint for a dossier.

If they are not Rapporteur, Co-Rapporteur or Peer-reviewer, large agencies usually dedicate some resources to scrutiny all the dossiers in order to perform an informed vote. However, considering their increased workload, they can no longer have the same level of involvement in all dossiers. Some dossiers are therefore more particularly scrutinised, depending on the following criteria:

- If the dossier present any specific scientific interest. The Swedish agency, for instance, assigns an internal assessor, for any dossier containing a new chemical entity;
- If potential risk for public health has been identified;
- If Rapporteur and Co-rapporteur teams disagree.

But NCAs mention also some reasons not to accept a Rapporteurship (question 10.2), mainly the following ones:

- unsustainable additional workload;
- unavailable expertise.

All NCAs **pointed out the lack of resources** as the main reason that limits their involvement in EMEA activities. This point is discussed later.

NCAs are fully aware of the positive impact of EMEA activities on their own functioning

NCAs pointed out many types of impacts of their involvement at EU level on their functioning, their scientific developments and the way they proceed at national level.

All NCAs, and in particular smaller ones, are considering centralised dossiers as good opportunity for their staff from a scientific point of view. Committees meetings should not be reduced to the official discussions. Informal interactions are also of high importance for representatives, notably with regard to **the learning process of smaller agencies**. Break-out sessions allow people that are more interested by a given application or specific issues to discuss with European colleagues.

Some NCAs are pointing out the **positive impact of EMEA work on the quality of national procedures**. This is particularly true for new Member States. The connection to national procedures is also essential for the work at the EMEA: especially for referrals or pharmacovigilance issues.

All NCAs are taking other types of benefits from their involvement in EMEA activities:

- Electronic databases (see the paragraph about the effectiveness of the Secretariat supported by telematics);
- **Interactions with the industry.** On this later point, small NCAs may not have any interaction with big pharmaceutical companies at the national level. The EMEA offers therefore an opportunity for them to interact with these important stakeholders;
- Personal communications with other representatives are also very important for NCAs, because they may face similar problems at national level. NCAs of new Member States may face difficulties with old authorised products that may lead to referrals because of limited documentation. The EMEA offer a place to discuss such topics directly with national experts from other Member States.

These new Member States pointed out some other sets of advantages:

- better understanding of decisions and how these decisions are taken ;
- increased availability of pharmacovigilance information.

At the end, NCAs estimate the return on investment regarding their involvement in EMEA activities as clearly positive, in terms of scientific interest, but also in terms of exchange of experience on the other hand. The EMEA offers the opportunity to experience different interpretations and ways of thinking, not only from a scientific point of view.

However, NCAs face important internal constraints to maintain their contribution to EMEA

NCAs are finding alternative means to maintain their involvement in EMEA activities such as the use of external experts or the focus on specific fields of expertise

More than 90% of NCAs state that they currently face a lack of resources to dedicate to EMEA-related activities (question 12.3.1) and to mutual-recognition and decentralised procedures as well (question 12.3.2). This is mentioned by NCAs as the main obstacle to apply for more Rapporteurships.

As mentioned, depending on their status, NCAs are dependant on other institutions. Some of them are allowed to decide on their own resources. In the current economic situation, public fundings tend to decrease and offer therefore less flexibility to NCAs.

A **limited involvement** in EMEA activities, whether through Rapporteurship or other related activities as for example working parties, has been identified as the first possibility to manage the shortness of resources (see Figure 55).

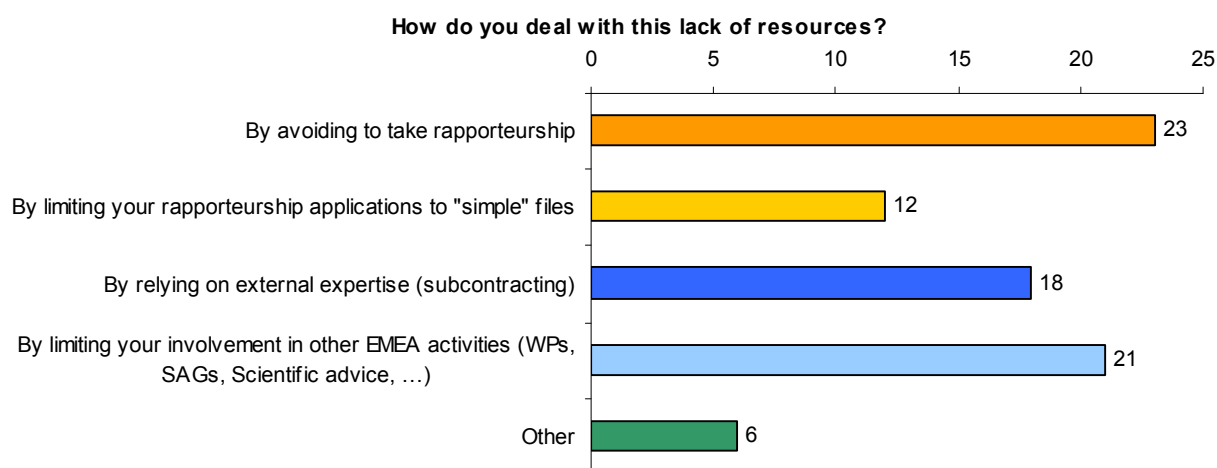


Figure 55: Question 12.3.4 If so, how do you deal with this lack of resources?

Source: Ernst & Young NCA questionnaire, June 2009

A second possibility used by the NCAs is to **rely on external experts** to conduct some part of the EMEA assessments. The ways, in which those external experts are mobilised, varies slightly between NCAs:

- Larger NCAs, that have more in-house resources, have no need to use external contractors. However, in rare occasion, it may happen, in case a specific expertise is required. NCAs consider that they have to maintain a certain level of in-house expertise and are reluctant to call for external expertise. External experts are very helpful on a scientific point of view, but are not very much aware of the regulatory and administrative requirements. It may cause additional work for the NCA. Thus, most NCAs take Rapporteurship only when they have relevant expertise in the agency;
- For smaller agencies, using external contractors may occur more frequently. In this case, NCAs prefer to rely on their local network (question 14.3) than on building international team by finding experts in other NCAs (see above). In some cases, external experts may even contribute to working parties: as for the large NCAs, some risks have been identified regarding the knowledge sharing and the sustainability of such contributions (see the focus at the beginning of the answer to the first evaluation question).

A third solution has been identified according to the feedbacks of the NCAs. Given their limited resources, some NCAs tend to **focus on specific scientific fields of expertise**, where they have some well-recognised experts. It is the case for small agencies that are not able to cover all therapeutic areas.

While smaller agencies are clearly in this situation, since they cannot have experts in all therapeutic areas for instance, larger agencies cannot give up specific expertises. These NCAs need however a full spectrum of expertise at national level and they prefer to keep an informed vote on all topics at EMEA level. For the same reason, large agencies consider their participation to all working parties as necessary.

The specialisation of national agencies could be theoretically a convenient global solution to the lack of resources. But, this evolution cannot be considered at national level: the need to have a full range of expertise at national level prevents specialisation.

In this context, NCAs face important difficulties to cope with non-fees related activities

70% of NCAs consider that the fees received from the EMEA compensate (almost) fully the costs incurred by the initial assessment work (question 11.1). Almost half of them estimate that the fees compensate less than 75% of costs incurred by post-authorisation activities (question 11.2).

The main problem in the funding of EMEA-related activities relies in non-fee related activities. The whole compensation process is very complex (see above). We noted that:

- NCAs have the feeling to be poorly compensated for the referrals (see Figure 56) compared to the volume.
- some NCAs contributions remain unfunded (paediatric, orphan) by EMEA reimbursement and are de facto covered by national resources. This is sometimes perceived as problematic.

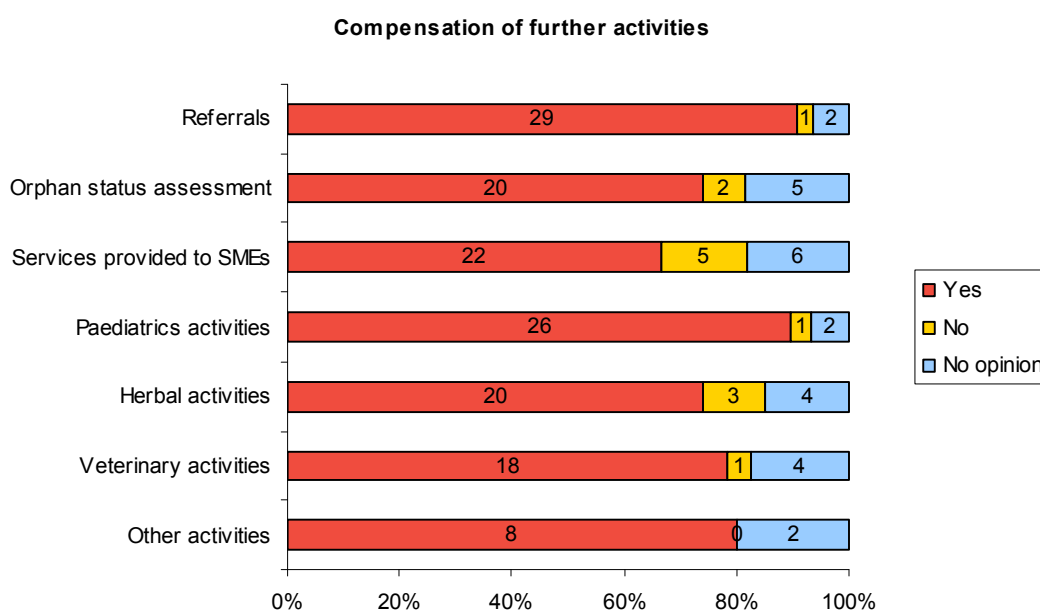


Figure 56: Answer to the question: “In your opinion, should the following activities be compensated?”

Source: Ernst & Young NCA questionnaire, June 2009

The issue of non funded activities is even stronger for NCAs which are essentially financed through fees. This is especially the case for veterinary agencies because of the fee reduction.

In both UK agencies, business is split according to the different sources of funding. One of the big challenges is to find financial resources for non-fee paid activities. As an example, the human agency, (MHRA) is assessing that the work related to unremunerated assessments amounts £2,8Mio of in 2008 (estimation based on full costs). Participation in committees is estimated at £1.5Mio.

The Hungarian human agency (OGYI), “middle active agency”, estimates the loss related to its involvement in EMEA activities as 7% of the total incomes of the agency, with the following breakdown:

- Loss of income due to missing working days: 560 working days out of office, plus the preparation for the meetings: this corresponds in total to the full working time of 5-6 experts, i.e. circa 5% of the agency total budget;
- Expenses of work not paid by EMEA (referrals, harmonisation and paediatric procedure): in 2008: it corresponds to circa 2% of the agency’s budget.

Here again, the fiscal deficit is considered as more problematic for the assessment work. The agency considers the participation in Committees as “the price of the involvement in the European network” that is largely compensated by a gain in scientific knowledge.

Thus, unfunded procedures present some risks regarding the sustainability of NCAs’ involvement.

- The reimbursement of committee work may be questionable with regards to the network organisation: each Member State contributes to the network. However, the request for funding of performed assessment work is more legitimate.
- But, some NCA may demonstrate less involvement in non-fee activities.

The funding system of non fee paid activities should be clearly identified. A realistic funding should be associated to all types of assessment activities, whether through fees, European or national funding.

It is especially important as non-fee paid activities will increase in the near future (paediatric, orphan).

It appears necessary to ensure the sustainability of the whole system. This clarification will most probably require a strong political re-engagement of the Member States.

The EMEA is encouraging the development of the NCAs’ cost accounting system which may contribute to better identify the cost inherent to the non-fee raising activities. A study is on-going.

At this stage, some NCAs do not know their costs; they do not have the tools to calculate neither the costs incurred by their involvement in the EMEA nor the costs incurred by their national activities. It is often linked to their status and level of autonomy on budgetary matters. When a head-institution takes care of the NCA budget and when there is no analytical accounting process in place, the NCA has no mean to identify its costs.

Concerning other types of activities, like committees’ and harmonisation work, NCAs are more willing to view these activities as part of the Member States’ contribution to the building of the European authorisation system and to accept their financial impact on their budget.

Some means to encourage a better mobilisation of the NCAs network have been identified

On a short-term period, setting up international teams would allow sharing the work, but in this case, the administrative burdens are pointed out as a bottleneck

NCA's are reluctant to build international assessment teams, because they consider that such work require linguistic and physical proximity. Experts have to harmonise their views within the team and with the Co-Rapporteur. This coordination would be even more complicated with foreign experts.

Nevertheless, some **NCA's have already experienced work sharing with other agencies**. More than a quarter of NCA's have solicited other agencies to participate in assessment teams, but on a punctual basis: only two agencies report frequent collaborations (on more than 50% of the files) with other agencies.

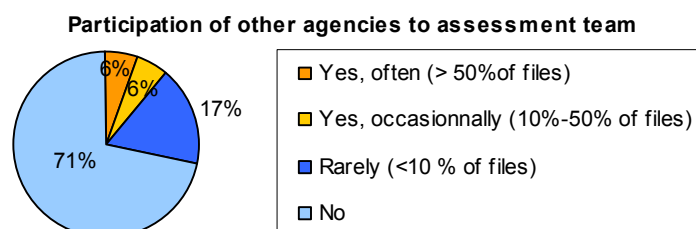


Figure 57: Question 15. Does your agency often solicit other agencies to participate to assessment teams?

Source: Ernst & Young NCA questionnaire, June 2009

Such arrangements are established notably through informal discussions at the Committees and by relying on pre-existing contacts (question 15.1). Some examples have been identified:

- France set up cooperation with Luxembourg, but it seemed to be an early attempt, considering some difficulties with coordination and reimbursement issues.
- Some NCA's lacking of specific expertise, asked the network for complementary inputs in the assessment dossier. For instance, the Estonian NCA asks for non-clinical expertise from other European NCA's in two of its centralised dossiers.
- The Hungarian veterinary agency has also reported an external cooperation with the British agency, but faced internal difficulties to reimburse the British experts.
- The Portuguese human agency took part several times in shared assessment work: with Finland, the British agency or Hungary.

The EMEA Secretariat should facilitate the coordination of such inter-agencies work. The improvement of existing EMEA teleconferencing tools could help NCA's to work with experts from other European agencies (see section 5.2.1).

NCA's underline the **administrative burdens** (fees distributions, contracts) as the main difficulty encountered to share the work with other agencies (question 15.2).

EMEA dossiers are planned sufficiently in advance to find the relevant complementary expertises in the network. Such collaboration could therefore be promoted by the EMEA Secretariat, including for scientific purposes.

To overcome the administrative burden for cross payments between NCA's, the EMEA could consider organising the direct payment to each NCA that contributes to the assessment team behind the rapporteur and co-rapporteur, relative to a pre-set distribution of activities (for instance efficacy/safety/quality parts of the dossier) agreed between NCA's.

National experts' mobility is another proper way to develop interactions between agencies. All experts who have experienced secondment at the EMEA in London pointed out that their experience allow them to build strong relationships with the Secretariat but also with other NCA's that are very helpful for further cooperation.

A broader mobilisation of the network could also be encouraged by a split in the assessment between Quality, Safety and Efficacy, made possible by the EMEA Secretariat through dedicated fees payment. While this could be a pragmatic solution for some assessment dossiers, NCAs remain reluctant towards a systematic split. System's flexibility is dear to NCAs.

On a longer-term perspective, the EMEA should support the gradual process of building up NCAs

Considering NCAs lack resources, most solutions have to be found at the national level as presented above. However, the EMEA Secretariat has a role to play regarding the building of the network in some aspects.

There is a gap between being a simple member of the EMEA and being a regular contributor. Smaller steps have therefore have to be considered in-between. New and smaller Member States should be helped to gain proper skills and confidence in order to be ready to take Rapporteurships.

Indeed, the involvement of NCAs in EMEA activities is also a question of trust and confidence: trust of the other Member States and confidence of the contributing NCA

The EMEA Secretariat should organise and support this gradual process. The following focus is identifying some steps that may help NCAs to increase progressively their involvement.

Hungary : best practices to increase NCA's involvement in EMEA activities

Hungary entered the European Union and the EMEA officially in 2004, but attended the committees already during the pre-accession phase. This country is recognised for its pharmaceutical tradition, on the industry but also on the academic sides. This facilitated the increase of their involvement within a short period. The human agency (OGYI) identified also good practices that could inspire other NCAs.

The following success factors have been highlighted during the interviews:

- ▶ To involve a person with strong leadership, who is able to follow the EMEA assessment work and identify the appropriate opportunities and who is adapted to the agency skills. The role of committee representatives is decisive in the extent that they link the committee activities with the national agencies;
- ▶ A progressively increasing involvement:
 - 1. by choosing first to be Peer reviewer: being peer-reviewer is a good training to get proper skills for dossiers assessment;
 - 2. by applying for Co-rapporteur: taking Co-Rapporteurship is an important step for NCAs. They may start with products that the agency is familiar with, like biosimilars;
 - 3. Rapporteur comes at the end, when the NCA feels sufficiently confident and has proper expertise to deal with the assessment of whole dossier.

The EMEA Secretariat should bring some support at these various stages of this gradual process, notably when NCAs take Co-Rapporteurship. The relationship between Rapporteur and Co-Rapporteur is almost a monitoring and sponsoring process that the EMEA should encourage. A broader allocation of Co-Rapporteurship should also be promoted by the appointment procedure, in order to support this process (as it is the case for the CVMP).

Trainings are already part of this strategy:

- Trainings provided by the EMEA Secretariat are very highly valued and NCAs are clearly requesting further development of such initiatives (see the part on the support of the EMEA Secretariat);
- The EMEA participates to the BEMA (Benchmarking of European Medicines Agencies) network, which has the objective “to contribute to the development of a world class medicines regulatory system based on a network of agencies operating to best practice standards”. This program is promoting the sharing of good management and assessment practices between NCAs.

Training arrangements between NCAs could also be supported by EMEA Secretariat through logistic facilities for instance. As an example, the British human agency (MHRA) cooperates already with Malta and Czech Republic; there also are also collaborations between the French veterinary agency and other veterinary NCAs. HMA is currently developing a broader training strategy.

The voluntary system has been appreciated by the NCAs for its flexibility

In general, NCAs consider the **voluntary system a relevant system** for the involvement of the EMEA network. Indeed, **it introduces flexibility** and allows each NCA to choose the best suitable way of involvement, depending on its level and types of expertise and resources. It is identified as strength of EMEA organisation.

The majority of NCAs (question 12.3.5) do not plan to reconsider their involvement in EMEA activities. These are identified as a priority for national agencies. **68% of NCAs consider the system as sustainable** (question 12.4). The main factors questioning this sustainability might be the increasing workload, first of all at national level and secondly at EMEA level.

In addition, **38% of NCAs would be able to increase their involvement in the EMEA system** and 47% marginally (question 12.6). It is well recognised that the vast number of assessment work is done by a small number of Member States. A larger involvement of “NCAs with currently limited activities” could therefore lead to a more balanced allocation of workload. This could be considered on a rather long-term period considering the time needed for NCAs to become fully operational.

On a short-term perspective, while NCAs consider the voluntary system as globally sustainable, some adjustments relating to the EMEA funding system and the way NCAs are paid could participate in supporting NCAs involvement in the context of resource constraint.

5.3. Long term effectiveness on EU citizens

*To what extent has the EMEA achieved its mandate to protect public and animal health by providing **the EU citizens** with human and veterinary medicinal products fulfilling the basic requirements for quality, safety and efficacy?*

Summary:

EMEA first objective is to promote the protection of public and animal health. This is achieved firstly through the quality of scientific evaluation as demonstrated previously, but requires also the support of the development of medicinal products of major therapeutic interest, the promotion of access to said products throughout the EU, the promotion of generic entry (see 4.4), taking appropriate measures to guarantee the efficiency of market surveillance and, at a wider level, ensuring a good level of practices harmonisation (through guidelines) as well as patients' and healthcare professionals' information.

On the whole, it can be said that EMEA uses in an effective and pragmatic way all these means to **enlarge and increase its positive contribution to public health, while respecting its limited scope of competences in some areas.**

As far as it falls within its scope of competence, EMEA does promote access to safe, efficient and high-quality drugs.

Regardless of the access itself, EMEA has put **constant efforts** into adapting to scientific evolutions and ensuring that European citizens and animals, including specific populations, are **provided with medicinal products of major therapeutic interest.**

The reliance on multiple specialized Scientific advisory groups, as well as the recent creation of three specialized committees (Committee for Orphan Medicinal Products, Paediatric Committee and Committee for Advanced Therapies) are evidence of such efforts.

- The Committee for Orphan Medicinal Products is generally considered a success, as it implemented effective incentives to promote **development and marketing of medicinal products for orphan diseases.** However, its sustainability may be put at stake both because the system may not appropriately compensate NCAs for their involvement, and because of potential evolutions, such as Personalised Medicine which could end up in the multiplication of potential Orphan status designations. Moreover, it is generally thought that veterinary products for Minor Use Minor Species should benefit from similar measures as medicines for orphan diseases, as the MUMS status has not enjoyed the same success as the orphan one.
- The introduction of the **Paediatric regulation** intended to ensure that safer and more innovative drugs were made available to children patients. This regulation has introduced new and stringent constraints on both the industry and EMEA resources. After a phase of adaptation, both stakeholders seem to be on their way to adapt to this evolution. However, from an operational point of view, **concerns remain on the status of PDCO vs. CHMP.** Indeed, PDCO ability to decide single-handedly on a Paediatric Investigation Plan may eventually impact availability of drugs for children, as it may diverge from CHMP final opinion, given years later. **Coordination** between PDCO, CHMP, COMP and SAWP should thus be enhanced to complete EMEA efforts regarding specific patient populations.

In addition, by allowing through the centralised procedure, a **relatively affordable marketing authorisation procedure**, EMEA offers the opportunity for global access to medicinal products for all citizens throughout the Member States.

However, it must be noted that **medicines' distribution falls out of the EMEA scope**, which is regretted by some stakeholders. Indeed, **access to medicinal products remains an issue in countries where the range of marketed pharmaceutical products is narrower and generally for certain veterinary products.** While the centralised procedure, as well as the promotion of generics, may compensate some of these difficulties, smaller Member States may nonetheless lack the

appropriate incentives to convince the industry to effectively market medicinal products that have been centrally approved.

Beyond its ability to promote medicines of major therapeutic interest, EMEA should also ensure that citizens are provided with the **right level of safety both before and after marketing authorisation of products**. This is done through guidelines production and post-authorisation activities.

- **EMEA guidelines are considered useful and valuable** both by the industry, which can rely on them to enhance product development's predictability and by evaluators, who rely on them as a means to better ensure harmonisation of assessment practices. Although a better dialogue between industry and working parties may need to be encouraged during guidelines production, guidelines overall reach their objective of promoting practice harmonisation, thus paving the way for better medicinal products for European citizens.
- **Pharmacovigilance**, on the other hand, has received a lot of attention recently, and is undergoing major changes at the EMEA level. **Specific difficulties have been identified both at the data collection, storage and analysis level**. Some of these difficulties are taken into account in the Proposed Amendments to strengthen and rationalise the European Community (EC) Pharmacovigilance rules and systems established by Directive 2001/83/EC and Regulation (EC No 726/2004). Although it is generally recognised that huge efforts have already been invested in the conception and realisation of **EudraVigilance database** and important achievements have been reached, **however** EudraVigilance remains a complex system to manipulate for the end-users and is still the subject for improvement from an end-user point of view, the end-users being either NCAs or the industry. Although it is clear that EudraVigilance development must continue, as a coherent European Pharmacovigilance data management system is absolutely necessary, however simplification of the system, partial evolution of the architecture in order to make the data available for management and analysis in ways that may seem easier to use, would ensure a satisfying level of trust in future broader Pharmacovigilance activities.

Although EMEA generally has a very positive and increased impact on EU citizens, it may **fail to communicate with them properly**.

EMEA generally suffers from a **lack of visibility** both from the patients' and the healthcare professionals' point of view. Although EMEA communication strategy does make use of all the **relevant channels** (from specialised information like EPARs to more wide-reaching media like its website), **their impacts remain limited**. Efforts need to be made on making a better use of the existing means of communication (for instance, increasing the awareness of EPARs' information for healthcare professionals) as well as adapting the information to targeted populations (for instance, simplifying the use of EMEA website³⁵).

Importantly, EMEA communication strategy is heavily dependent on its networks, especially NCAs. As **NCAs are the local relays for EMEA information**, their involvement in EMEA communication strategy is crucial.

The following analyses that allow answering the evaluation question are structured around four main types of analyses.

- 1. Availability and distribution of high quality, safe and effective medicinal products (5.3.1)
- 2. EMEA support to the development of product of major therapeutic interest (5.3.2)

³⁵ The launch of a new website is scheduled for Q1 2010, which should significantly improve this situation.

- 3. Guidelines contribution to harmonisation and access to medicinal products (5.3.3)
- 4. EMEA contribution to patient safety and to the quality of post-authorisation marketing: impact of pharmacovigilance and other post-authorisation activities (5.3.4)
- 5. EMEA contribution to better information of EU patients and healthcare professionals (5.3.5)

EMEA first objective is to promote the protection of public and animal health. As we have seen before, this is mainly achieved through maintaining a very high level of quality of scientific evaluation.

However, public and animal health goes beyond evaluation per se, and it is EMEA responsibility that, not only EU's citizens and animals have access to high quality, safe, and efficient medicinal products, including those of major therapeutic interest, but they also benefit from a wider system that ensures harmonisation of practices before and after evaluation, as well as a stringent surveillance of the market post-authorisation. We will deal with each of these topics, before turning to communication towards patients' and healthcare professionals' information, which is also a means of promoting public health at a wider level.

5.3.1. Availability and distribution of high quality, safe and effective medicinal products

EMEA is responsible for the protection of public health and thus is concerned with the availability of high quality, safe and effective medicinal products on EU territory. However, access to medicines and their distribution do not strictly fall into EMEA scope of responsibility, as industry is not compelled to introduce a centrally approved medicinal product on all Member States territories, and distribution monitoring is under the Member States' responsibility, apart for parallel imports monitoring.

We will nonetheless explain how EMEA contributes, through some of its activities, to a better access to medicinal products. As we have seen earlier, all EMEA activities converge in making high quality, safe and effective medicinal products available to EU's citizens and animals:

- guidelines production (see 4.4.3.) contribute to harmonisation of good practices, which in turn lead to a safer and more efficient development and marketing environment for medicinal products;
- the Centralised Procedure allows a facilitated and simultaneous access to innovative and generic medicines to all EU markets, at a competitive cost (see 5.1.1 and 5.4)
- the quality of evaluation guarantees the quality, safety and efficacy of marketed medicinal products (see 5.1.1),
- pharmacovigilance and other post-authorisation activities (see 5.3.4) contribute to the quality, safety and efficacy of the same products after they have been introduced on the European market

However, there remain some concerns regarding effective availability of certain medicinal products in some EU countries, especially those with an already small range of marketed pharmaceutical products and smaller markets. Although the centralised procedure has decreased some of the costs related to submitting a market authorisation in these countries, industry still often refrains from effectively marketing its products when the market is considered too small (and thus not covering the global costs incurred). Reasons invoked include the costs of translating medicinal products leaflets as well as logistics, material and administrative difficulties (e.g. new negotiations with local reimbursement agencies). Although EMEA has no responsibility over the latter, reconsideration of translation requirements has often been called for by the industry. The facilitation of generic entry on the European market has allowed some Member States to access medicines that were not available before, but this does not settle the issue of lack of access to innovative medicinal products. Parallel distribution may sometimes allow the introduction of such medicinal products, but it remains anecdotic.

Parallel distribution for centralised products is the only distribution activity in which EMEA has a direct responsibility. Parallel distribution is the distribution of a centrally authorised medicinal product from one Member State to another by a pharmaceutical company independent of the marketing-authorisation holder. EMEA is responsible for checking compliance of products distributed in parallel with the conditions laid down in Community legislation on medicinal products and in the marketing authorisation of the product.

EMEA parallel distribution activities have significantly increased since the introduction of generics into the centralised procedure, as can be seen in Figure 58. While EMEA ability to deal with notifications in time was repeatedly raised as an issue before 2006, it has consistently improved since then (2005: 148 days, 2008: 35 days, with a self-imposed target of 48 days).³⁶ However, this timeframe is still superior to the legal timeline of 30 days. It is also interesting to note that most applications for notifications now end up with notifications being issued, which was not the case before 2006. It seems that applications' quality and compliance with rules have improved. Such improvements are likely due to the implementation of Regulation 726/2004 that clarified the legal basis for the notification of parallel imports and made it clear that it was EMEA responsibility to check that the conditions laid down by Community legislation were respected.

Moreover, as a first step to put in place a process to verify compliance of parallel distributors with the mandatory notification procedure and the notices issued by the EMEA, EMEA has included parallel medicines in its 2009 Sampling and Testing plan. This should contribute to ensure the safety of patients relative to parallel imports medicines.

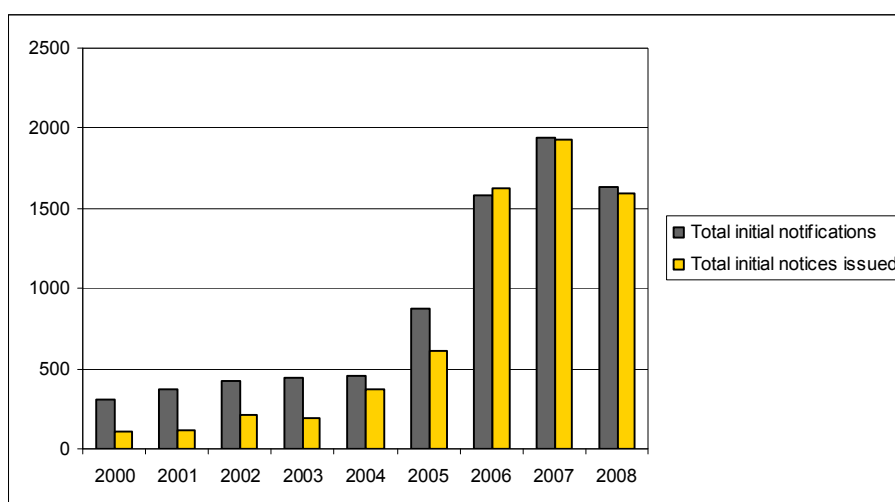


Figure 58: Evolution of parallel distribution notifications by EMEA from 2000 to 2008 (notifications, validated and finalised)

Source: EMEA annual reports (2000, 2001, 2002, 2003, 2004, 2005, 2006, 2007, and 2008)

5.3.2. EMEA support to the development of medicinal products of major therapeutic interest

The promotion of the development of medicinal products of major interest has been an important goal for the EMEA since its creation. The recent creation of the Committee for Orphan Medicinal Products (COMP, 2000, operating since April 2001), the Paediatric Committee for Medicinal Products (PDCO,

³⁶ EMEA, Annual Reports 2005, 2008

2006, operating since July 2007) and the Committee for Advanced Therapies (CAT, 2008, operating since January 2009) show the commitment of the Commission and EMEA in addressing the specific issues raised by each type of medicines and in promoting innovation and access to medicines addressing the needs of specific populations of patients. At the Secretariat level, 55 persons are devoted to supporting Scientific Advice, Orphan and Paediatric activities. All these activities have been shown to contribute to the promotion of medicinal products of major therapeutic interest.

EMEA orphan medicines activities have proved successful in promoting research, development and introduction of new medicines for orphan diseases

The COMP is often referred to as a “success story”

The COMP was created in 2000. Its principal task is to examine applications for designation of Orphan Medicinal Product status. This status is meant to encourage companies and people who intend to develop medicines for diagnosing, treating or preventing rare (so-called “orphan”) diseases.

This status grants the applicants various incentives for the product they develop: market exclusivity for 10 years, facilitated access to Scientific Advice (protocol assistance) to optimise development (e.g. clinical design) and guidance on preparing a dossier that will meet European regulatory requirements, access to Centralised Procedure and Fee reductions for all types of centralised activities (application for marketing authorisation, inspections, variations, scientific advice). Moreover, the status may facilitate eligibility for specific EU funding for research projects.

In itself, the legislation thus gives specific advantages to Orphan products which are mainly enacted through EMEA, and more specifically COMP and the Secretariat services devoted to Orphan products (7 FTEs inside the Scientific Advice and Orphan Drugs Sector).

Both the industry and other stakeholders tend to agree that the creation of COMP and related incentives have had a positive impact on research and development for specific products for orphan diseases. The procedure showed immediate success, with 83 submissions in 2001. This number has increased until 2005, when it stabilized around 120 submissions per year (with the exception of 2006, see Figure 59).

This coincided with a global increase and stabilisation in the number of authorised medicinal products for orphan diseases, with an average of 12,5 new medicinal products/year receiving approval from the CHMP for orphan diseases during the 2001-2008 period (range: 7-18, vs. only 2 in 2000).³⁷

It is interesting to note that very few negative opinions have been given by the COMP (see Figure 59). This may be due to the relative high number of withdrawals, generally because the medicine would not be considered as fitting to the orphan designation criteria. However, the careful consideration of whether a population can be considered as an orphan population may become a more complex issue in the future. Indeed, the trend towards the development of targeted therapies and personalised medicine could lead to more and more segmentation of patient populations into sub-populations. The rationale for such segmentation should be carefully monitored, as these subgroups may end up meeting the criteria for orphan status, while being sub-indication of a non-orphan disease. More applications of this type may lead to an increase of COMP's workload in the near-future.

³⁷ EMEA, Annual Reports 2001-2008

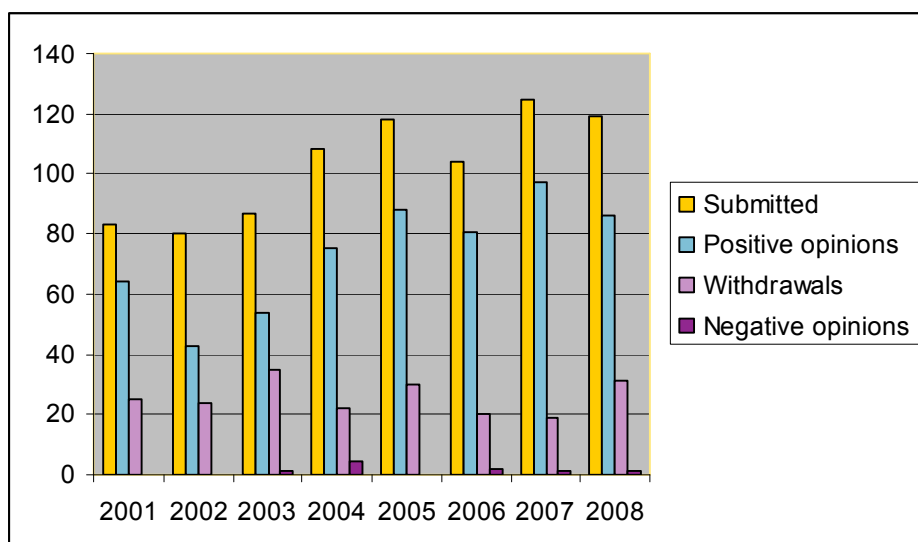


Figure 59: Evolution of the number of submissions for orphan product designation and COMP opinions from 2001 to 2008

Source: EMEA annual reports (2000, 2001, 2002, 2003, 2004, 2005, 2006, 2007, and 2008)

Since its creation, COMP has always delivered its opinions in time i.e. less than 90 days.³⁸ In terms of internal organisation of the Secretariat, although the process now seems to be well in place, the management of resources may however be complicated by the inherent irregularity of the applications. The assessment of Orphan status also is of interest as it is the first domain where the Secretariat has been directly involved in scientific activities. EMEA Secretariat has the responsibility to prepare the assessment for the COMP. As of today, most stakeholders, both from the industry and COMP sides, have recognized the efficient and valuable work provided by the Secretariat on orphan drugs. This may be considered an encouragement to enhance Secretariat scientific activities in the future.

In terms of coverage of patients' conditions, most therapeutic areas have been covered by orphan product designations since the creation of COMP, showing that the procedure is of use for very different conditions, although rare cancers do lead the number of designations (see Figure 60).

³⁸ EMEA annual reports, 2001-2008

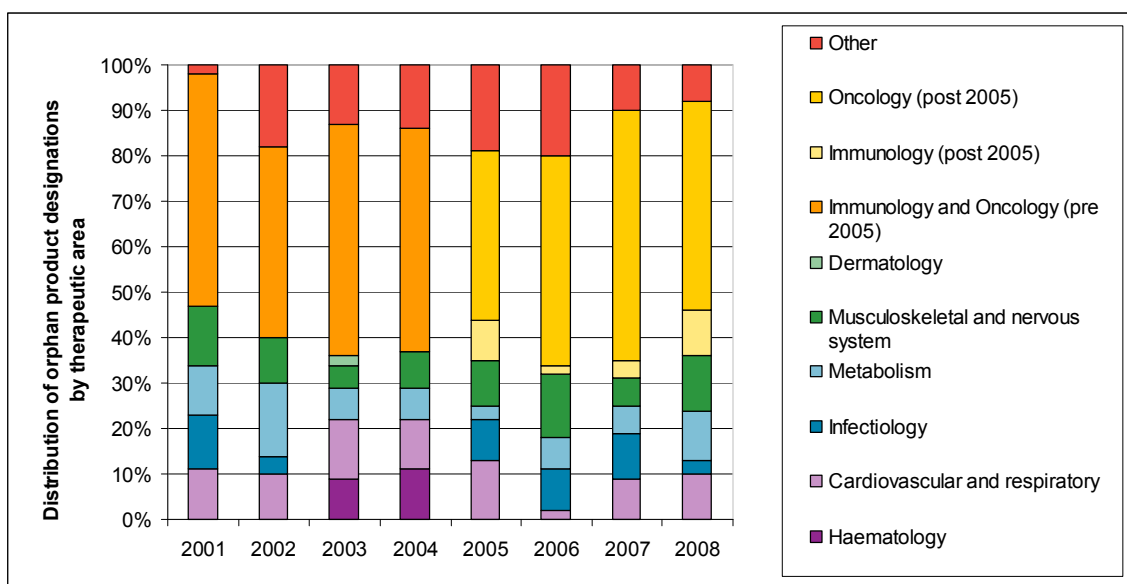


Figure 60: Evolution of the distribution of designations for orphan status by therapeutic area. Until 2005, oncology and immunology applications are taken together, and then the figures discriminate between both, showing dominance of oncologic conditions

Source: EMEA annual reports (2000, 2001, 2002, 2003, 2004, 2005, 2006, 2007, and 2008)

To conclude, although the current orphan products policy is unanimously recognized as having very positive outcomes, most stakeholders have expressed their concern over two subjects.

First, some interviewees doubt the sustainability of a system that does not allow directly Rapporteurs and Co-Rapporteurs' compensation and which budget has significantly increased in recent years. In 2008, the EU special contribution for Orphan medicines reached €6 millions (vs. €600 000 in 2001 and €4.982 millions in 2007), of which 61% were used to cover protocol assistance (scientific advice, which is given free of charge for products with an orphan status) and 31% to cover marketing authorisation costs (orphan products enjoy a 50% fee discharge in that case). Out of 27 respondents on that question in the questionnaire administered to NCAs, 20 asked for compensation for the evaluation of orphan status (2 said it was not needed and 5 gave no opinion). Some interviewees also reported that some NCAs adopt strategies to take Rapporteurship mostly on compensated activities, thus potentially leading on the long term to difficulties in dealing with the orphan and paediatric assessments.

Second, although orphan medicines do reach the market more easily than they used to, their reimbursement is a raising issue at the national level. While this matter does not strictly enter the scope of the EMEA, the unwillingness of national reimbursement bodies to pay for medicines that end up being very expensive and treating a very small population may on the long run undermine EMEA efforts to provide all patients with new and accessible medicines.

“Orphan” medicines in veterinary medicines: the impact of the Minor Use - Minor Species (MUMS)

Minor Use - Minor Species (MUMS) medicines may be considered to be the veterinary equivalent to orphan medicines for humans. The creation of the MUMS distinction is intended to stimulate development of new veterinary medicines for minor species and for rare diseases in major species which would otherwise not be developed. The 2004 legislation included provisions to assist potential applicants seeking to authorise veterinary medicinal products for limited markets. Although there is no legislative definition of minor species, CVMP has defined major species according to animal population data and total consumption figure (EMEA/CVMP/477/03-Final). These include cattle, sheep, pigs, chickens, salmon, cats and dogs. All other animal species are minor species. Minor uses are defined as the use of

veterinary medicinal products for the treatment of diseases that occur infrequently or in limited geographical areas. CVMP considers minor uses on a case-by-case basis, considering prevalence/incidence of the condition and geographical spread of the condition with the EU.

The CVMP is responsible for granting the MUMS status to a given medicine. This status confers the applicants' special incentives, as is the case for orphan medicine status. As is the case for SMEs and orphan status applicants, EMEA provides MUMS applicants with a greater level of advice and assistance in relation to applications for marketing authorisation (pre-submission meetings and free procedural advice). SME applicants with MUMS status also benefit from free scientific advice, as well as reduced data requirements and assistance with translation of the product information documents. They may also be granted a fee waiver or a fee reduction for MRL applications (especially if it is a MRL extension to minor species). Since 2009, MUMS status applicants may also benefit from fee exemption in the event of failure of validation and fee reduction for inspections (if SME) and for authorisation and maintenance (equivalent to a generic fee).

All these incentives do contribute to the promotion of development of medicines for MUMS. However, a major difference between MUMS and Orphan status is the absence of market exclusivity for the former. This, in addition to the fact that smaller markets for veterinary medicines are of course less lucrative than human ones, may explain why the MUMS status does not enjoy the same success as the orphan one. Indeed, in 2007, the CVMP only granted two free scientific advices for MUMS and received two applications following these free scientific advices. In 2008, CVMP granted one marketing authorisation for a MUMS product as well as one post-authorisation activity with reduced fees. CVMP also granted one MRL application and one line extension with reduced fee for MUMS products. At this stage, both interviewees and annual reports wonder whether an adequate incentive for MUMS remains to be enacted. Market exclusivity may be such an incentive.

The lack of a convenient status for bees, in particular, is sometimes reported as worrisome, since this very important, but small in population, species is currently endangered but not many companies engage in developing adapted medicines, since it would not be profitable.

Stakeholders still need to adapt to the requests and challenges of the paediatric regulation

The Commission recently put in place the paediatric regulation in order to enhance access to medicines that would be specifically designed and tested for children. The new legislation has imposed new demands on the industry in terms of product development, and at this stage it may be said that the various stakeholders (industry, Secretariat and PDCO members) have not fully adapted to these evolutions, although progress is reported at all levels.

The Paediatric Committee (PDCO) was created in 2006 and held its first meeting in July 2007. The PDCO's main responsibility is to assess the content of paediatric investigation plans and adopt opinions on them in accordance with Regulation (EC) 1901/2006. The PDCO is not responsible for marketing-authorisation applications for paediatric medicinal products, but it may be requested to prepare an opinion on the quality, safety and efficacy of a medicinal product for use in the paediatric population if these data have been generated in accordance with an agreed paediatric investigation plan.

The Paediatric Regulation has made it compulsory for companies to submit a Paediatric Investigation Plan (PIP) to the PDCO before engaging in the development of a medicine intended for children. This means that no paediatric medicine can be submitted for marketing authorisation in the European Union if it has not followed a pre-approved PIP. The PIP is aimed at ensuring that the necessary data is gathered, through appropriately safe and ethical experiments, to support the authorisation of a given medicine for children.

The PDCO is entirely responsible for accepting or refusing that development plan, which should include timing of children studies as well as detailed information on the medicine (including paediatric formulation). This decision is, at this stage, completely independent of CHMP's opinion. It is also independent of any scientific advice that the applicant may have asked for.

The principal limitation raised by stakeholders regarding the PIP is precisely the risk of incoherence between the opinions produced by the PDCO, the CHMP Scientific Advice and later on the CHMP itself.

This topic is covered elsewhere (see 5.1.3 and 5.4) but is a major source of concern for the industry, although observers note that coordination is currently improving between the SAWP and the PDCO, as well as between the PDCO and the CHMP.

It seems advisable that the Secretariat should play a greater part in the future to ensure true consistency and communication between these three entities. This seems all the more feasible that the same Sector is responsible for both Paediatric and Scientific Advice activities.

More generally, the organisation of work for the PDCO and the relative services inside the Secretariat has proven being difficult, the new legislation generates an important workload for both.

The PDCO treated 88 initial procedures and 5 re-examination procedures in the last 6 months of 2007, the number rising to 286 initial procedures in 2008 (and 11 re-examinations). The number of applications still tends to increase (on the first 6 months of 2009, there were 152 initial procedures treated).³⁹ As the submission of PIP is compulsory, this is an indicator that companies are indeed increasing the number of molecules they develop specifically for paediatric use and that the Paediatric Regulation has had a positive effect on Paediatric medicine development.

This success does not go without adjustments. Secretariat staff reports that there are currently around 30 to 40 submissions per month, and the 20 staff assigned to Paediatrics are having difficulties coping with the workload. From an organisational point of view, EMEA Paediatric Secretariat services were initially staffed with only 6 people. This number quickly grew to adapt to the first underestimated complexity of the files (although their number had been correctly predicted), but is still considered insufficient.

As is the case for the Orphan products, the Secretariat has a very important role in assessing the PIPs and preparing the work for the Rapporteurs and Peer-reviewers. This level of scientific implication and support may explain the increased involvement of usually less active Member States in taking rapporteurship and peer-reviewing responsibilities, as they can rely more on EMEA expertise in this case (see Figure 61). PDCO members are chosen for expertise rather than in order to ensure all Member States representativeness, but paediatric rapporteurships and peer-reviewing activities shows a better distribution among countries than may be seen in other committees. France and Germany, the most active contributors in 2008, managed respectively 15% and 12.6% of the files, which left space for many other Member States to participate. Thus, the PDCO may prove a committee where less actively experience and visibility can be gained, by acting both as Peer-reviewers and Rapporteurs for dossiers.

³⁹ EMEA Secretariat statistics

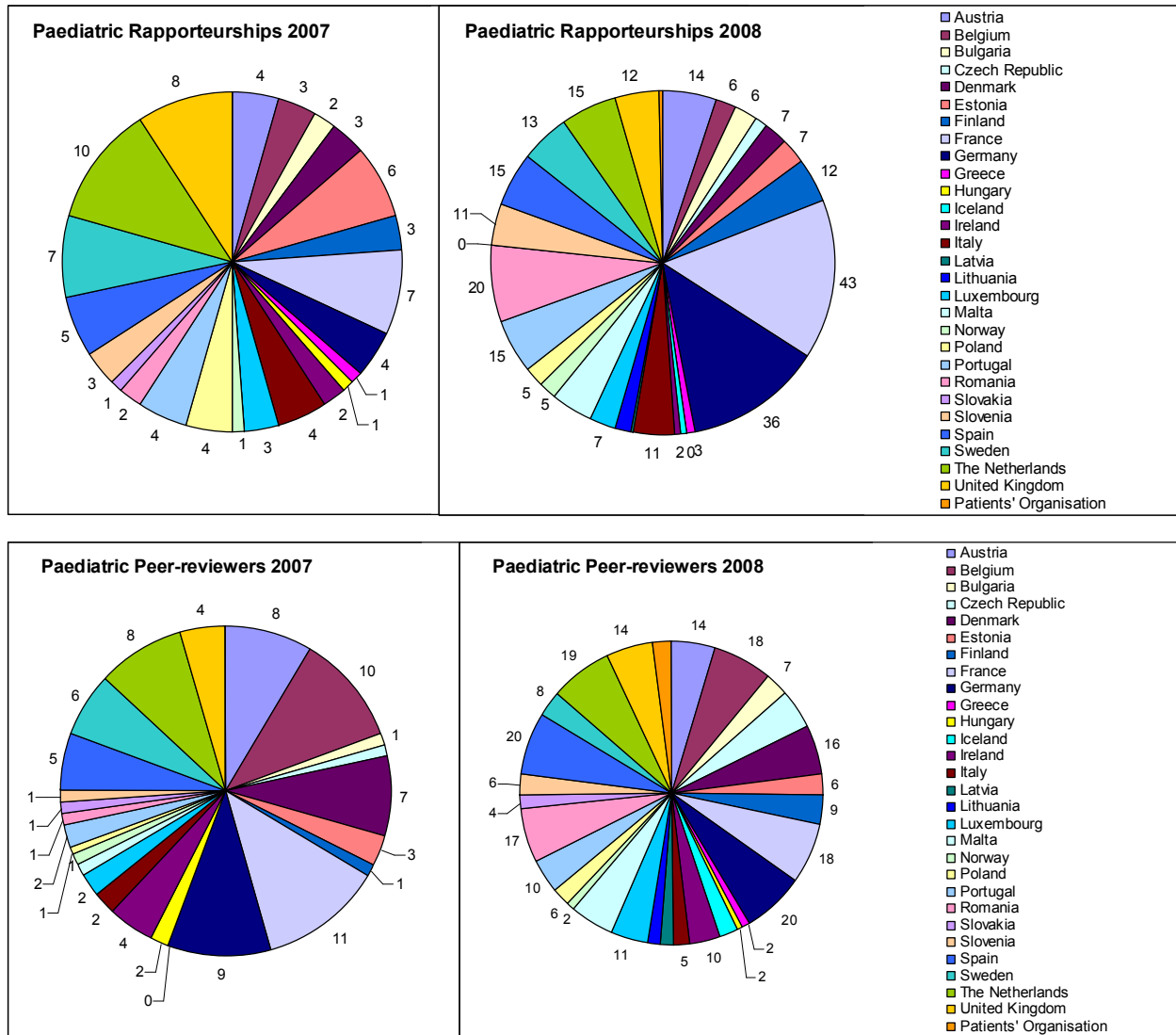


Figure 61: Distribution of PIP Assessment Initial Procedures Rapporteurships and Peer-reviewing amongst the Member States in 2007 and 2008: an increasing number of Member States are getting involved, especially for peer-reviewing

EMA annual reports (2000, 2001, 2002, 2003, 2004, 2005, 2006, 2007, and 2008)

Independent of the number of applications, industry representatives tend to complain that the procedure is very heavy and that the requirements made by the PDCO may not always reflect what is feasible from a product development perspective. In particular, some industry interviewees suggested that the high proportion of clinicians at the PDCO makes it more likely that requests are based on an ideal of “what product development should be”, rather than on more pragmatic views based on what current product-development technologies allow. While this criticism may be due to a difficulty and/or a reluctance to adjust to new and demanding legislation, the PDCO and Secretariat have recognized having experienced some difficulties in this regard, and are currently trying to adjust themselves.

Some observers note that the first legislation was enforced without sufficient communication between the industry and the legislators: although the industry was invited to participate, the discussions may not have covered all the subjects, and some have arisen with practical cases. Moreover, all stakeholders, including at the EMA, tend to underline that the procedure could be simplified, and that a better

collaboration between PDCO, SAWP and CHMP should be promoted, so as to avoid any potential contradiction between these various bodies' opinions on the long run.

Some recommendations can be drawn in this area:

- Engage in a common consultation with NCAs regarding the compensation of Orphan and Paediatric activities, together with a planning of needed resources and competence in the 5-10 years to come.
- Beyond the reports on implementation requested by the legislation, realise a survey about the *impact* of the paediatric legislation after two years (also include a focus on potential simplifications and Secretariat support to industry in explaining and providing guidance). This may also include a clarification of PDCO's responsibilities and role vis-à-vis the industry and the CHMP, by putting in perspective the impact of PDCO's opinion vs. CHMP final opinion, as well as potential overlaps with SAWP's Scientific advice (see previously 5.1.3).
- Promote Secretariat's role in ensuring the circulation of information and coherence of opinions and advices between PDCO and SAWP, as well as PDCO and CHMP.

Promote industry/PDCO members dialogue, and, if considered necessary, re-evaluate the composition of PDCO to balance clinicians with persons with more thorough medicine development experience, while guaranteeing independence.

- Launch a reflection on the appropriateness of market exclusivity or other incentives for MUMS products.
- Launch a reflection on the middle-to-long-term impact of personalised medicine concepts (e.g. smaller and more well-defined patients' population) on the orphan status designation.

5.3.3. Guidelines contribution to harmonisation and access to medicinal products with a satisfactory level of efficacy, quality and safety

EMA guidelines include:

- Regulatory guidelines (not discussed here),
- Scientific guidelines related to Quality, Safety and Efficacy, adopted by the scientific committees
- Good manufacturing Practice (GMP) guidelines
- Good clinical practice (GCP) guidelines and conduct of clinical trials guidelines
- Good distribution practice (GDP) guidelines
- Good laboratory practice (GLP) guidelines
- Orphan medicinal products designation guidelines
- Maximum residue limits guidelines
- Pharmacovigilance guidelines
- Herbal medicinal products guidelines
- EDQM and the European Pharmacopeia documents (not discussed here): product-specific guidelines for quality control of medicinal products for human use derived from blood and vaccines.

EMA guidelines are expected to provide both the industry and the assessors with sufficient and appropriate guidance in order to guarantee good efficacy, quality and safety of pharmaceutical products at all stages of development as well as after their introduction on the market. They contribute both to the promotion of public health and to the harmonisation of European evaluation and medicine development practices.

As a means of harmonisation, guidelines are also expected to facilitate assessment and to decrease the risk of referrals by making expectations more explicit for both applicants and assessors. Eventually, they should contribute to limiting the evaluation workload.

Guidelines production is highly resource-consuming. Guideline production is the main activity of some WPs. Some WPs were responsible for less than 10 guidelines, but other dealt with dozens: in 2008, the CHMP Biosimilars WP managed 19 documents and guidelines, the Blood Products WP dealt with 26 and the Pharmacovigilance WP with 25, the CHMP Safety WP manages 44, the CHMP Biologics WP manages 57 and the CHMP Efficacy Working Party managed as many as 227 documents and guidelines. Maintaining, updating and creating new guidelines thus represent an important workload for the Agency.

Guidelines contribute to a better harmonisation of assessment and enhance predictability for the industry

In most cases, guidelines are recognized to provide added value to stakeholders and to contribute to harmonisation.

This is supported by NCA respondents to our questionnaire, who underline that EMA has a very important impact in terms of guidelines for their countries (see Figure 62). It is also interesting to note that the reasons for taking Rapporteurship include the fact that it allows to participate first hands in

guidelines production (27 out of 28 agencies rating it important or very important) as well as to get up-to-date knowledge on regulation and guidelines evolution (27 out of 20 agencies rating it important or very important).

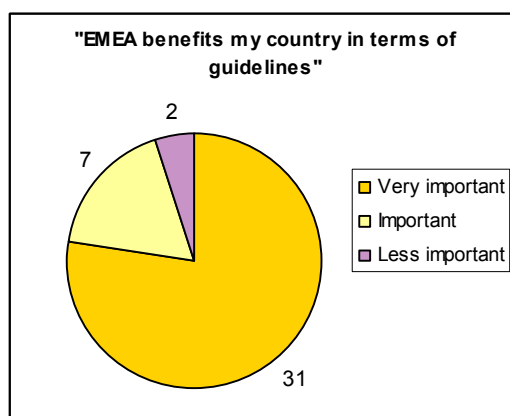


Figure 62: Question 4.2. What benefits does the EMEA provide for your country in terms of guidelines?

Source: Ernst & Young NCA questionnaire, June 2009

EMEA guidelines are in line with ICH recommendations, and are generally more specific. EMEA guidelines thus contribute to harmonisation both at the European and global levels. More generally, NCAs and especially smaller ones, insist that EMEA guidelines are extremely important to help provide a high-level common ground for practices and assessments. The fact that all Member States end up contributing to guidelines also increases their legitimacy at the national level. Guidelines are considered as the basics of evaluation by many assessors. They complement ICH guidelines, and provide a reliable frame for NCAs' work.

Guideline topics and number mostly fulfil both NCAs' (see Figure 63) and Industry expectations. In the questionnaire administered to NCAs, most respondents thought that the number of guidelines is appropriate (27 out of 37) and their topics fit the needs (34 out of 37). This opinion is generally shared by the industry. However, some interviewees stress that guidelines' adequacy with needs may vary widely depending on the therapeutic area: there are for instance many guidelines in the central nervous system or cardio-vascular therapeutic area, but maybe less in other domains, like gastro-enterology, endocrinology or medicines for elderly people.

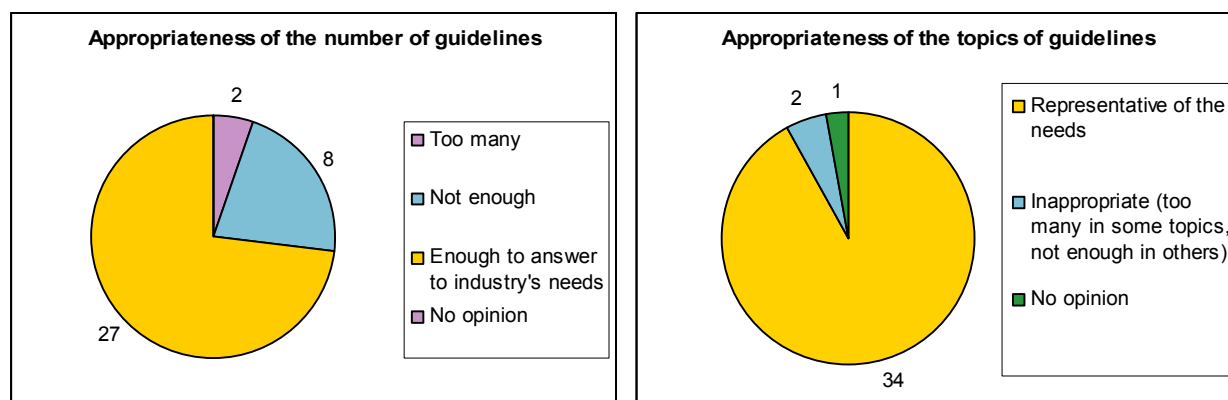


Figure 63: Question 18. Concerning EMEA-produced guidelines, would you say there are...?

Source: Ernst & Young NCA questionnaire, June 2009

Both industry and assessors underline guidelines' contribution in allowing them to work within a coherent framework. They also suggest that considerable improvement in medicinal products quality and safety (in particular on the clinical side) have resulted from EMEA guidelines activity in recent years, and that many potential sanitary crises have been avoided. The fact that guidelines are regularly updated also contributes to their quality and their impact.

However, as guidelines are produced by various working parties, their level of detail may vary, as well as their length and their explicitness. Indeed, the level of prescriptiveness of guidelines and their wording are of utmost importance to all stakeholders, as they enable readers to draw a unique interpretation or not. Any lack in this regard leads to potential misinterpretations or divergence between NCAs, assessors and industrials and may produce referrals. It is often noted that not all guidelines are equal in their prescriptiveness. On the other hand, there is a risk of ending up with too prescriptive and numerous guidelines that would overload companies with irrelevant requests. Some interviewees have suggested that at least for generics there is a concern over guidelines complexity, whereas the products themselves are simpler. This opinion may however not be shared by all.

The industry generally gives positive feedback on guidelines, although some specific improvements may be called for. Industry does see guidelines as a support to product development and marketing authorisation submission. There is a demand from the industry to get good and informative guidelines, so as to improve procedures' predictability (both in terms of timing and outcomes). This avoids any decisional delay during development or difficulty during the assessment process. However, as guidelines are by definition at least partly outdated when they are used, industry representatives also stress the need for guidelines to be flexible enough to anticipate on scientific evolutions and/or assessors that will not stick strictly to the guidelines if the science or the technique has evolved. Both points may prove difficult, the first because having a prescriptive but still flexible wording is an achievement in itself, the second because it may be considered as putting the harmonisation role of guidelines at stake.

Guidelines are clearly of considerable importance to SMEs, but sometimes impose challenges on their limited resources and competences. This makes EMEA procedural support and scientific advice to SMEs all the more valuable.

As guidelines are produced by various bodies, some inconsistencies may also appear. Reducing inconsistencies by improving the monitoring of the impact of guidelines on each other may further enhance guidelines' compliance. Moreover, guidelines' validity needs to be challenged regularly to avoid outdated information, but the current updating rate is generally considered sufficient (sometimes even too fast).

The guidelines production process is quite efficient but may benefit from more fruitful interaction with stakeholders

It is widely recognized that writing a "good" guideline is a complicated matter. Indeed, guidelines should be precise enough to allow only one common interpretation, while keeping enough space for evolution and specific situations. This difficulty emphasized the importance of following an efficient process.

The current process for the preparation of guidelines is considered to be generally good. After a need for new guidelines or updates has been identified (for instance because the committee has seen a few files raising the subject and, if necessary, asked for a reflection paper), a selection of topics is included in the relevant work program. Each WP work programmed is revised at least once a year. The concerned WP then appoints a rapporteur and, if necessary, a co-rapporteur. This rapporteur, together with a small selected team, will then draft a short concept paper (2 pages), to be submitted to the concerned working party. If the WP considers the concept paper to be of high priority (as compared to other topics), it is then adopted and released for consultation (over a 2 to 3 months period), so as to gather comments. The appointed team then takes these first comments into account to prepare an initial draft guideline. The

resulting draft is then released for consultation for another 3 to 6 months to allow for comments by both the industry and other stakeholders. The final draft, which should take gathered comments into account, is then written and submitted to the relevant committee for adoption and publication. Guidelines are usually implemented within 6 months of their publication.

This process allows for a good selection of the guidelines that need to be prepared and generally, the rate of update is considered satisfactory. Guidelines are revised approximately once every 5-10 years, depending on the evolution of the science and the industry (ex: bioequivalence: first version in 1991, revised in 2001, next revision undergoing, expected to be published in 2010). Every year, each WP establishes a list of guidelines to be updated. These are rated for their importance and urgency. A revision may take a few months but could also be as long as a normal guidelines writing (i.e. 18 months to 2 years). The decision to make a revised guideline can be postponed for months or years until the data or the context is considered compelling enough to justify such an update. Updates are considered adapted to the needs at this point, but some stakeholders would like to see a more explicit tracking of what aspects of a given guidelines have changed after updating (i.e. a kind of “track-change” monitoring). Another minor improvement would be to add, in a separate document, real cases and precedents to illustrate the guidelines purposes.

In terms of difficulties encountered with the process of preparing guidelines, it is still the case that some regulators are considered by the industry as having a too theoretical approach to the writing of guidelines. The process does include a consultation with the industry, and sometimes even involves focus group meetings participating to working parties. However, industry representatives still emphasize that they would appreciate getting more involved in the preparation of guidelines. Some industry representatives also complained that they sometimes did not get enough feedback as to why a comment given during the consultation phase was taken into account or discarded.

However, the situation has seen significant improvements in the past few years, with EMEA even producing guidelines on the way to interact with industry for the past 4-5 years, which has contributed to a real interactive dialogue. The recent introduction of concept papers (including the consultation phase) and focus group meetings are also considered a significant improvement in EMEA-industry dialogue on guidelines. All stakeholders also welcome specific initiatives like workshops that gather both EMEA, academics and industry representatives (e.g. Workshop on Bioequivalence for veterinary medicinal products).

Industry also calls for an improved dialogue between scientists from each side, some citing cases where the industry thought to have presented scientifically sound reasons not to do something and did not understand the refusal they were opposed. It is also the case that some regulators or scientists may not have a long-term view. Apart from the consultation and focus group meetings, industry also asks for more transparency on the way guidelines are written. However, it is also important to bear in mind that at this stage, drafting takes 6 to 12 months, including industry consultation. A longer schedule, for instance including a longer consultation period for drafts, may affect guidelines’ timeliness with regards to science evolution.

Industry involvement in guidelines production could also find its limits in the necessary independence of evaluators and scientists when setting the standards. Indeed, some interviewees have suggested that one of the reasons why ICH guidelines are less specific is precisely because they involve industry representatives more directly, and thus entail more compromises.

More generally, although guidelines are there to promote harmonisation, assessors should also bear in mind that some scientific evolutions or industry innovations may justify to occasionally stray from them: industry often complained that some assessors tend to follow the guidelines too closely even when some additional data could justify different development plans.

Some rooms for improvement have been identified in this area:

- The transparency of the procedure could be made more straightforward by fixing the timelines and making the decision process more explicit (both at the committee level and at the working

party level when deciding not to take into account a given comment)

- Guidelines could be clarified by presenting case studies along with their publications, as well as underlining major changes after an update
- Adaptability of assessment could be improved by proposing trainings or annual “up to dates” for guidelines which will not be revised in the upcoming year. This may allow assessors to have up-to-date knowledge regarding science or technologies that may conflict with existing guidelines.
- More effort could be put in monitoring the way a new guidelines may impact others, and communicating on potential effects. This could be assumed by the Secretariat.
- Positive initiatives promoting industry’s relevant involvement in guidelines dialogue should continue (focus groups, specific workshops, consideration of comments, respect of the consultation period)

EMEA is completing its activities on medicinal products of major therapeutic interest through Scientific Advisory Groups and the recent creation of the Committee for Advanced Therapies

Scientific advisory groups (SAGs) and the recently-created Committee for Advance Therapies (CAT) also both contribute to a better understanding and promotion of innovation and to the introduction of medicines of major therapeutic interest through the diversity of subjects they can deal with.

SAGs are established by the CHMP to provide advice in connection with the evaluation of specific types of medicinal products or treatments. They are not subjected to any representativeness constraint and they consist of European experts selected according to their expertise in a given subject (most often a given therapeutic area). They generally meet on request. To date, CHMP can rely on 7 advisory groups, namely SAG on Cardiovascular Issues, SAG on Anti-infectives, SAG on Clinical Neuroscience, SAG on Diabetes and Endocrinology, SAG on Diagnostics, SAG on HIV/Viral Diseases and SAG on Oncology. SAGs are widely recognized by stakeholders to contribute to EMEA high level of expertise in edge. The fact that there is, for instance, a SAG on Diagnostics is an indicator that EMEA is taking into account new trends of medicinal product development and the emergence of fields like Personalised Medicine.

The CAT, which first meeting was held on 15/16 January 2009, has been created to answer the needs of emerging fields (or advanced therapies), in particular gene therapy, somatic cell therapy or human tissue engineered products. The CAT should support scientifically sound development of such advanced-therapy medicinal products. It is too early to draw conclusions on CAT activity, but CAT already has held several meetings with learned societies and industry to identify available and lacking expertise in the network, to understand expectations and to spot bottlenecks in the existing context.

The creation of the CAT, the availability of a wide panel of experts through SAGs, as well as the implementation of PDCO and COMP on the whole show the ability of EMEA to adapt to science evolution and to go on facilitating European citizen’s access to safe, efficient and innovative medicinal products of major therapeutic interest.

5.3.4. EMEA contribution to patients' Safety and to the quality of post-authorisation marketing: impact of Pharmacovigilance and other post-authorisation activities

Pharmacovigilance activities contribute to patients' safety and are undergoing major evolutions

Pharmacovigilance has received a high amount of attention by the Commission and other EMEA stakeholders recently. Indeed, pharmacovigilance and other post-authorisation activities are of the utmost importance to guarantee citizens with a high level of safety and quality of medicines once they have been approved.

Although it is widely recognized that Pharmacovigilance activities have improved thanks to EMEA involvement in the past years, there remains space for simplifying pharmacovigilance processes and making them more efficient, improving pharmacovigilance-related communication and increasing stakeholders' involvement at various levels (including patients' organisations).

We will discuss the state of pharmacovigilance at this point, bearing in mind that multiple discussions and propositions are undergoing at present, in particular the recent "Proposed Amendments to strengthen and rationalise the European Community (EC) Pharmacovigilance rules and systems established by Directive 2001/83/EC and Regulation (EC) No 726/2004" suggest multiple improvements to pharmacovigilance activities, and also raise the possibility creating a Pharmacovigilance Risk Assessment Advisory Committee.

Data Collection, storage and treatment: specific difficulties may arise on the field

The first step in Pharmacovigilance is the collection of data by healthcare professionals and national competent authorities (NCAs). EMEA is not directly responsible for this phase, but is responsible for coordinating the collection and gathering the data under a unified database, EudraVigilance.

Data collection is one of the points of concerns for Pharmacovigilance at this point, both for human and veterinary medicinal products, albeit for different reasons.

The data collection itself is the responsibility of Member States and the industry, and most stakeholders consider that it should remain so, as NCAs are closer to patients and local contexts. NCAs themselves are particularly insistent over it, as they consider it is their responsibility to have a detailed knowledge of adverse events occurring on their territory.

EMEA has however expressed concerns regarding the compliance of both NCAs and the industry with reporting timelines. EMEA also expressed concerns regarding the quality of reporting. Two contradicting views are opposed regarding this observation. On the one hand, EMEA underlines that it has put important efforts into providing both NCAs and the industry with IT reporting tools and associated training, that should allow for a very good compliance and understanding of EudraVigilance functioning, EMEA also has raised the topic with Member States (at HMA) and will invest substantial efforts in improving the quality of data contained in the database by launching a call for tender for outsourcing data cleaning (6,5 million euros to be invested in the next 4 years).

On the other hand, users from NCAs and industry alike often reported that EudraVigilance remains a complex system to handle, where data management may seem difficult. It is important to acknowledge that EudraVigilance mission is very complex, since it has to deal with huge amounts of data and make it available on line to various stakeholders under significant IT security pressure. EudraVigilance specifications have to deal with its primary objective of enhancing public health, with different users expectations (at the Secretariat, NCAs and industry level) and with architecture limitations. To fulfil these objectives, the development and operation of EudraVigilance is overseen by the following committees:

- The EudraVigilance Expert Working Group (EV-EWG) and the EudraVigilance Steering Committee (EV-SC): these fora are composed of experts in the field of pharmacovigilance with

representatives from NCAs, the pharmaceutical industry, non-commercial sponsor clinical trial organisations and the EMEA. They are responsible for defining business requirements in line with the legal framework defined in Community legislation and for co-ordinating all implementation aspects.

- The EudraVigilance Telematics Implementation Group (TIG) operating under the EU Telematics Management Structure, including experts from all NCAs in the EEA. The TIG is responsible for the technical aspects of the implementation of EudraVigilance.

However, and although EudraVigilance has been built under both the auspices of these committees and EU Telematics Strategy, thus involving all relevant stakeholders in the process at the management level, this evaluation still observed difficulties at the user level.

Beyond NCAs and industry, there also is a concern on the field that some adverse events may not be reported, especially in the veterinary sector. The reasons involve a lack of information of concerned stakeholders (breeders, veterinary health care professionals) or even fear about potential consequences (e.g. potential loss due to livestock quarantine etc.). This has important consequences, especially considering the recent introduction of the notion of Reference Product in the veterinary sector. Indeed, NCAs tend to doubt an absence of Pharmacovigilance track record for products that have been introduced many years ago, as they know that Pharmacovigilance reporting is scarce. They tend to be more vigilant when the molecules are usually distributed in high volumes (e.g. antimicrobials). This situation leads to a lack of trust in foreign products, and consequently to NCAs launching referrals when generics of said products are introduced in a third country. Recently, efforts have been made to improve this situation, for instance through the publication of the document “Veterinary Pharmacovigilance in the EU - a Simple Guide to Reporting adverse reactions” (CVMP, adopted June 2006). However, these efforts have remained insufficient to ensure proper reporting to date.

Despite important achievements, feedback on EudraVigilance still shows difficulties experienced at the user level

EudraVigilance collects pharmacovigilance data on a daily basis from all EU Member States authorities and from companies and clinical trial sponsors, while complying with EU data protection legislation. It was the first system in the EU to operate according to the international guidelines on electronic data⁴⁰. In building EudraVigilance, EMEA has led the development of international standards for electronic exchange (ICSR) of case reports and identification of medicinal products. EudraVigilance receives an average of 45,000 reports per month. The data is then available for analysis by the EMEA staff and by relevant authorities from the Member States.

EudraVigilance has already shown important achievements in terms of supporting automated, rapid and secure electronic exchange of case reports between registered users (more than 20 000 000 transactions since 2001, according to EMEA sources). EMEA reports that the database availability to Member States and EMEA is above its objective of 98%. EMEA has also put in place the EudraVigilance Support Program in January 2009 to provide Member States with EudraVigilance Reaction Monitoring reports for selected medicinal products.

While 2119 analyses are conducted using EudraVigilance per month⁴¹, many interviewees have reported difficulties in performing analysis using EudraVigilance data. From the NCA point of view, data is accessible but may seem difficult to manage. From the industry point of view, they acknowledge that much information is conveyed to the system however it is difficult to perceive the output at the industry level. EMEA informed us that a soon-to-be-published study about EudraVigilance validation shows that using EudraVigilance results in an increase of 40% of detected safety issues. NCAs will probably benefit from the consultation of such a study, and may also use it as a benchmark for a better use of EudraVigilance. At this stage, there remain difficulties.

⁴⁰ International Conference on Harmonisation-ICH

⁴¹ Source: EMEA, figure for both EMEA and Member States combined

This is especially true of big agencies that already had a pre-existing Pharmacovigilance system, including a database. Notwithstanding potential compatibility difficulties between old systems and EudraVigilance system (which generally have been dealt with in the past few years), these agencies generally consider that EudraVigilance does not yet provide them with information as accessible and/or as useful as their own. While this may be due to difficulties adjusting to a novel system, a more user-based approach to further evaluation of EudraVigilance may be considered: it seems that although NCA management was directly involved in EudraVigilance evolution, users still face difficulties in every day manipulation of the database. This has also been reported by Marketing Authorisation Holders. This slow take-off of the system and perceived lack of effectiveness are of major concern, undermining some stakeholders' confidence in the upcoming initiatives relative to Pharmacovigilance as well as in the ability of EMEA to manage European-wide IT systems (even if EMEA also runs a number of other telematics projects such as EudraNet, EudraLink, EudraCT, EudraGMP etc. most of which are considered very efficient while others may experience difficulties).⁴² In some cases, the disappointment is all the more important that stakeholders are very much aware of the high level of input and efforts (including financial) put by EMEA, NCAs and the European Commission in the EudraVigilance, as well as the multiple updates and modifications already implemented.

There is general agreement on the fact that EudraVigilance development must continue, as a coherent European Pharmacovigilance data management system is absolutely necessary. All stakeholders agree that such a centralised system is of utmost importance to implement a robust and coherent European pharmacovigilance policy. However, many questions remain as to how to simplify the system and maybe evolve part of the architecture in order to make the data available for management and analyse in ways that may seem more sensible to users. Many users regret that the architecture and ergonomics of the system are not more directly adapted to their needs and make navigation complicated rather than straightforward. While it is clearly a difficult matter to settle, as users differ in their needs at the Secretariat, NCA and industry levels, and reorganisation could be deemed too difficult, we could at least suggest that the support that EMEA provides to all stakeholders concerning EudraVigilance⁴³ should be reconsidered in the light of such experienced difficulties.

On the other hand, there also seems to be a need to increase efforts from both NCAs and the industry to adapt to EudraVigilance.

Independently, EudraVigilance still poses difficulties of harmonisation as well as interpretation at the national level. It is a challenge to adapt EudraVigilance to the European lack of harmonisation in certain respects (name of molecules, double entries, variations in the way and dosage of administration, variation in the quality of reports etc.). There is an important need of competent resources to clarify these variations in a scientifically-sound way. The reported challenges in analysing the data held may be partly due to these difficulties, and to technical limitations. More generally, there is a need for an international standard on the identification of medicinal products. This would definitely benefit the management of individual case safety reports in EudraVigilance, avoiding double-entries and incoherences. EMEA is involved in the development of such standards, and the proposed new legislation should provide the legal basis for the EMEA to collect data compliant with these standards from the industry, allowing a comprehensive medicinal products dictionary to be created.

Pharmacovigilance processes are complex and fast-evolving and industry may need additional and more transparent support to adapt

⁴² The complete list of telematics project run by EMEA is exposed earlier in this report. This list includes: EudraNet, EudraLink, EudraVigilance, EudraPharm, EudraCT, EudraGMP, Product Information Management (PIM), European Review System, Eudra User Security Management, EU Telematics Controlled Terms and Eudra Data Warehouse

⁴³ EMEA provides training for Member States: 184 experts from NCAs have been trained by EMEA on analysing the database so far, and monthly training courses should also take place in 2010. There also is training for companies.

More generally, pharmacovigilance processes are often considered too heavy and burdensome, in particular by the industry. The formalisation of procedures may have recently increased due to a stronger focus on pharmacovigilance issues. Moreover, EMEA/industry contacts relating to pharmacovigilance are currently limited to PSURs submission. This may leave the MAHs under the impression that pharmacovigilance is a “black box” where they give information but receive no direct or personalised feedback. A more supportive and pragmatic approach would thus be welcomed by MAHs. Indeed, industry representatives worry they will not be able to adjust to fast-evolving expectations without appropriate support.

However, recent proposals for the amendment of the legislation are expected to introduce simplification to the administrative work and clarifications of certain aspects. In particular, the proposed amendments to legislation suggest multiple alleviations of the pharmacovigilance burden for the industry. These include:

- single reporting by the MAH to the EMEA when a reporting requirement is triggered (including PSURs): this particular point may become a point of concern for NCAs if EMEA does not retro-transmit the information properly to NCAs through EudraVigilance or another system;
- transfer of the responsibility to monitor literature reporting adverse events from the MAH to the EMEA: this would allow for a wider and more organised monitoring, also preventing any double submission to the European Pharmacovigilance system, but will necessitate additional resources;
- adaptation of PSUR frequency depending on the expected risk: this goes along with the proposition of implementing specific measures of monitoring for medicines considered potentially more prone to adverse reactions than others;
- implementation of a master file for each company pharmacovigilance system (thus limiting the number of variations to be submitted if a modification of the PhV system occurs)

All these simplifications should be welcomed by the industry, as they make pharmacovigilance processes more straightforward. They should also decrease the Secretariat’s workload and prevent double-entries, thus eventually facilitating the good communication of information to healthcare professionals and patients.

Some concerns remain on the methodologies for using Pharmacovigilance data in a sound and effective way: more efforts should be put into optimising methodologies

Another major concern is the ability to make good use of Pharmacovigilance data, beyond alerts and suspension measures.

Even when the data collection and storage are not an issue (for instance in Member States where Pharmacovigilance has been managed for a long time) NCAs, industrials and healthcare professionals worry that the data may not prove easy to analyse. Even if it is very easy to identify when and where a given event occurred, there still remain debate on which criteria and thresholds should be used and how an event should be interpreted depending on the therapeutic area, the disease, the patient population, the type of molecules, etc. For instance, a case may not be interpreted in the same way whether it follows the administration of a vaccine or a small molecule, the timing of occurrence of adverse events may differ, the thresholds from which an alert should be given are different.

Many stakeholders agree that EMEA should take the lead in producing and implementing new quantitative and qualitative data analysis methodologies for pharmacovigilance as well as formalising decision processes. This should go with strengthening EMEA own competences in these areas. This is coherent with the leading role that EMEA has taken in an IMI project on Pharmacovigilance methods.

Effective pharmacovigilance processes should ensure safety for patients

The impact of pharmacovigilance activities on patients’ information is a major issue. Although EMEA there The recent “Proposed Amendments to strengthen and rationalise the European Community (EC)

Pharmacovigilance rules and systems established by Directive 2001/83/EC and Regulation (EC) No 726/2004” include further positive amendments from the patients’ safety and information point of view.

These include creation of a Pharmacovigilance committee, which would replace the Pharmacovigilance working party, would co-ordinate Pharmacovigilance and make recommendations on the safety of medicines to the CHMP. Although not the final decision maker, this committee would also hold hearings in case of Pharmacovigilance referrals. This committee would thus have an important impact, as it would analyse adverse events, but also likely be involved in the management of specific Pharmacovigilance situations or health crisis (specific epidemic situations, availability of specific treatments etc.). The crucial impact on such decisions at a local level may advocates for the necessity of having a committee that would keep representatives from all Member States. In this context, some stakeholders have expressed to us their concern regarding the scope of its responsibilities and its relationships with other scientific committees, especially the CHMP. These changes may impact both the way a medicine is evaluated and the level of transparency of the procedures from the pharmaceutical companies’ point of view.

While the creation of a dedicated Pharmacovigilance committee would probably favour a more streamlined coordination of Pharmacovigilance activities, many stakeholders have expressed their concern about a committee which would base its opinions solely on Pharmacovigilance data, without paying attention to efficacy data. In particular, many consider that any post-authorisation efficacy data, when available, should be taken into account, for fear of disconnecting the risk and benefit evaluations, which is the very basis of medicine evaluation. An interesting counter-example is given by the recent merge between ANMV’s (French veterinary NCA) Marketing Authorisation Commission and Pharmacovigilance Commission: these two commissions were merged precisely to ensure that Pharmacovigilance decisions should be more operational, and that they should take all the data into account.

At the same time, an interesting development that could partially compensate the risk of over-focusing on risks is the proposed extension of PSURs scope to become an analysis of risk-benefit balance of the medicinal product rather than a detailed presentation of individual case-reports.

Moreover, the potential decrease in CHMP workload that could come out of the creation of a new assessment body is clearly welcomed. Here again, as with other committees interactions, it is of the utmost importance that committees, as well as related Secretariat services, should keep an appropriate level of communication between them, so as to avoid misunderstandings or incoherence. More importantly, a decision based only on post-authorisation risk assessments, without taking into account correlated benefit and efficacy data, may hinder access to innovation for some patients.

To summarize, many initiatives are currently under way to put more efforts into an efficient, more streamlined and less burdensome Pharmacovigilance process. Much has already been achieved, and important efforts are being put into reaching that objective, and EMEA will probably need additional resources to assume a good centralised coordination of activities that have extended in scope.

- Importantly, there is a need to further improve EudraVigilance in order to ensure that this centralised system is able to provide Member States with data necessary to make informed decisions at their national level. This is necessary both from an effectiveness, efficiency, and communication point-of-view vis-à-vis the Member States, who already have invested a lot on this initiative.
- EMEA should also take the lead in improving Pharmacovigilance methodologies and analyses, in order to ensure that a novel focus on Pharmacovigilance should not come at odds with the ability to provide European citizens with innovative new medicines with a balanced benefit/risk ratio, both at authorisation time and a few years after.
- Considering this last point, a careful consideration of the responsibilities of the new future Pharmacovigilance body, connections with CHMP and evaluation criteria seems all the more necessary. From an organisational point of view, a pre-committee could probably allow the body to answer both the need for a representative committee, since Pharmacovigilance is a

subject of high importance to citizens and the need for the right level of competence (through co-opted members).

EMEA role in other post-authorisation activities, such as inspections is recognized

EMEA is responsible for the coordination of other post-authorisation activities for centralised products, in particular inspections. Most stakeholders consider that EMEA deals well with this activity, and underline that although there used to be issues of coordination between EMEA and NCAs in this regards, the problems have been solved. The number of EMEA-coordinated inspections has steadily increased in the past few years (Figure 64), roughly following the rate of increase in the number of centralised applications.

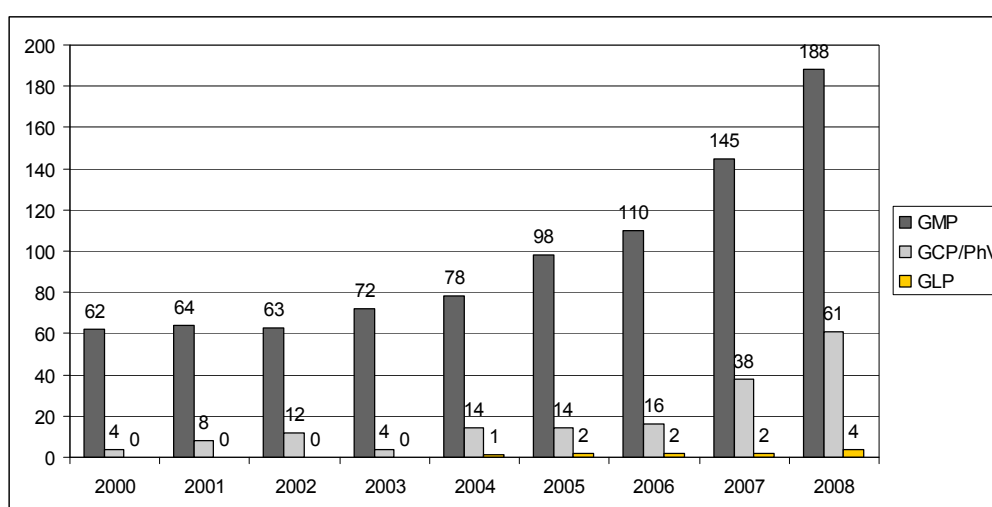


Figure 64: Evolution of the number of EMEA-coordinated inspections (GMP, GCP/PhV, GLP) from 2000 to 2008

Source: EMEA annual reports (2000, 2001, 2002, 2003, 2004, 2005, 2006, 2007, and 2008)

It is important to note that post-authorisation inspections and controls still depend heavily on Member States' legislation, and harmonisation in this regard still may have a long way to go. For instance, the responsibility for doing the controls may lay in different institutions (private or public) depending on the Member State, which in turns shapes the policy of the Member State in terms of post-authorisation expectancies. The reliance on national inspectors can prove an advantage in many cases, due to national contexts and languages, although the existence of multi-national teams is wished for on certain occasions, to provide a wider range of competences. Some interviewees have called for the ability to draw more straightforwardly on foreign resources when needed (for instance through the implementation of an appropriate and updated database of experts).

In the veterinary sector, a lack of resources at NCA level for dealing with the inspections has sometimes been reported.

Other post-authorisation activities of EMEA of course include variations, extensions, transparency procedures, name changes, re-assessment, renewals of authorisation, marketing and cessation notification, sunset clause monitoring, Article 46 paediatric study submission, transfer of marketing authorisation. These have been covered elsewhere in this report.

5.3.5. EMEA contribution to better information of EU patients and healthcare professionals

The EMEA dedicates resources to manage communications and networking activities

Communication activities (interaction with patients, healthcare professionals, the website, transparency, etc.) are carried out within the EMEA Secretariat, by the press office, the communication team in the executive support sector, the medical information sector, the operational units, etc. IT solutions to communication needs and publication of non-product specific information have been managed by the Communications and networking Unit (since EMEA reorganisation in end 2009 this unit has become Information and communication technology').

The communication of information is a critical point to assist the EMEA objectives. This part will evaluate to what extent the EMEA achieved its mandate to protect public and animal health. Thus, our study will be particularly focused on the information imparted to EU patients and healthcare professionals.

The result of the evaluation will firstly depict the communication mechanisms used for the groups targeted: EU patients and healthcare professionals. We will then assess the impact on the methods employed on the stakeholders targeted.

The mechanism used will obviously not have the same impact according to the stakeholders since each of them require different considerations. For example, while the media exposure might give a better knowledge to patients, a targeted communication through clear communications on EMEA website will be a better asset for the healthcare professionals.

The mechanism to employ to communicate will also depend on the message to convey: common meetings with patients group will increase confidence towards the EMEA while rapid alerts will be more effective to disseminate pharmacovigilance issues on the same population.

EMEA is using suitable mechanisms to inform healthcare professionals and patients, but some of those could be improved

EMEA exposure on media is low

It is generally perceived that the EMEA is suffering from a lack of public recognition, especially due to poor recognition in the media. However, some stakeholders believe that EMEA does not need to be visible, either because visibility doesn't directly serve EMEA objectives to protect patients, or since EMEA is not in the best position to have an efficient communication policy for the targeted public. Indeed, the follow-up of the NCAs is necessary to provide good media exposure for the EMEA. Yet, the NCAs do not feel this task is under their scope.

Reactive communication could be increased by making transparency procedures used in answers to request for documents more flexible

The EMEA must comply with the regulation 1049/2001 for access to the EU Institutions documents (applicable in December 2001). This regulation is being reassessed in 2008 through a proposal for a regulation of the European parliament and of the council regarding public access to European agencies.

Hence, the EMEA has worked on transparency measures since its creation, and in particular submitted new EMEA transparency policy measures in 2003 (adopted by the Management Board in 2004). A new draft has been proposed in June 2009 for public consultation.

Since 2006 though, only 68% of the requests for access to documents were fully accepted (source: EMEA annual reports). The protection of commercial interests of a natural or legal person (Article 3(2)(a) of the EMEA Implementing Rules) appears as the main justification for those refusals, while the protection of the Agency's decision-making process (Article 3(3) of the rules) is the second justification. Indeed, the intellectual & industrial property rules may not allow full transparency. However, some measures should be taken to improve this rate, and the balance between the competing interests of the industry versus the disclosure of product issues will be a main challenge for the transparency policy.

Besides, the Agency is undertaking measures to further improve the access to information for general public:

- The EMEA Secretariat is finalising the policies on access to EudraVigilance data (public consultation finished in March 2009) and later plans to grant access to pharmacovigilance data for the general public.
- Similarly work is ongoing to develop a module of the EudraCT database to provide access to specific data on paediatric clinical trials.

EMEA is currently improving the user-friendliness of its website

The website is a critical communication tool since it allows to inform the public, health professionals and the media about the EMEA activities, provide up-to-date information and advice and to display warnings.

Most stakeholders perceived that the EMEA website needs to be simplified to facilitate users' access to adequate information. Appropriate measures are undertaken by the Agency as regards to the public and easy availability to publish EMEA documents on the website, as well as to improve the pharmacovigilance aspects. Those measures should also implement easy links to others databases such as EudraVigilance and EudraCT. Globally, EMEA website is under reconstruction to facilitate search and access to information.

The proactive communication through workshops is greatly appreciated by the different stakeholders

The perception of the different healthcare professionals and patients groups with regards to their interaction with the EMEA is very positive according to the interviews performed.

The organisation of dedicated workshop, mainly thanks to the creation of the EMEA Human Scientific Committees' Working Party with Patients' and Consumers' Organisations (PCWP) and the EMEA/CHMP Working Group with Healthcare Professionals' Organisations (HCP WG), has greatly contributed to this high level of satisfaction.

Moreover, these groups have expressed their satisfaction to receive information on EMEA activities through mail (newsletter, meeting minutes ...) on a regular basis.

This proactive approach of the EMEA towards these stakeholders is allowing the Agency to get their input on the strategy for the future. It is also believed that it greatly contribute to the implication of these stakeholders in the consultation process, and offering them the opportunity to give their opinion. In return, these inputs are also appreciated from the Agency for different reasons. For example, even though it is assumed that the scientific expertise demonstrated by the patient group may be limited, their practical contribution is supporting the EMEA activities.

While the EMEA efforts look relevant, some limits exists to contribute into effective communication:

- The different organisations contributing to the PCWP or HCP WG are not participating to all workshops (for budgetary reasons or for limited interests). Even though the meetings frequency is

reasonable (4 times per year for PCWP in 2009 and 3 times for HCP WP), the agenda may be built in order to better optimize the different organisation participation. Meetings should be tailored to include information of particular relevance and interest to the groups concerned.

- ▶ The opinion expressed by the healthcare professionals groups, or the patient ones, might unfortunately not reflect the majority of healthcare professionals or patients perceptions. Indeed, a gap exists between the organisation and the population that they represent. This drawback will be further discussed in the conclusion of this part.

The available information is providing most product details

It is generally agreed that the transparency on products is essential, and particularly the reasons justifying a decision concerning a product authorisation. Indeed, it is the main action that makes stakeholders feel confident about the regulators.

EMA publications inform professionals on the decisions taken and their justification through many ways, and in particular:

- ▶ European public assessment reports (EPARs),
- ▶ Product information for centrally authorised medicinal products: summary of product characteristics (SPC) and package leaflet for centrally authorised products,
- ▶ Publication of ‘question and answer’ documents,
- ▶ Information on Community referral procedures.

It is agreed that most relevant information is made available to justify different opinions taken by the EMA.

The publication of the demonstration of comparative benefit of the approved drugs has been suggested as a potential improvement, especially for orphan drugs.

Efforts should also be continued on the capability of the Agency to disseminate information in all languages. Indeed, some countries regret that all information is not translated in their national languages.

Finally, a non negligible number of healthcare professionals and patients groups are highly interested in knowing whether a product has been centrally authorised and where it is marketed. Although CHMP publishes information on its website and communicates directly with NCAs on this subject, it seems that most healthcare professionals and patients have no knowledge of where to find that information.

As mentioned previously for the workshops organisation, the information provided should probably be more focused towards the target audience. While everybody agrees that most details are available, these should be attuned to the interest of the various target populations. It is also stressed that concerned stakeholders do not necessarily know whether a particular piece of information is available, even though said information may actually be conveyed on the website.

The EMEA is developing the mechanisms to communicate efficiently on pharmacovigilance issues

Healthcare professionals and patients are really concerned about the pharmacovigilance activities. The effective communication of alerts or product recalls is critical.

The specificities of the pharmacovigilance issues impose to use rapid mechanisms to circulate information. EDI (electronic data interchange) seems the most appropriate method to exchange these messages to concerned stakeholders. The EMEA is also prioritising the EUDRANET (European Telecommunication Network in Pharmaceuticals) to appropriately alert the different NCA.

It is therefore presumed that the EMEA, or the European Commission, shall continue to focus its strategy on the telematic initiative to interconnect the different NCAs to improve communication with regards to pharmacovigilance concerns. The EMEA, and the European Commission, should also continue to develop guidelines to strengthen this aspect of the communication.

Although, it is agreed that an effective strategy should necessarily go through the NCAs. Even though EMEA can and should inform directly “end users” stakeholders, its role should essentially consist of coordinating the communications of the Member States by maintaining appropriate portal on the safety of medicines. Consequently, it means that the efficiency of the communication on pharmacovigilance aspects depends on the ability of the NCA to successfully improve and maintain their communication to the concerned parties.

The effectiveness of the EMEA communication towards healthcare professionals and patients is highly dependent on other stakeholders (organisations, NCAs)

The mechanism used will obviously not have the same impact according to the stakeholders since each of them require different considerations. For example, while the media exposure might give a better knowledge to patients, a targeted communication through clear communications through the website will be a better asset for the healthcare professionals.

The mechanism to employ for communication will also depend on the message to convey: common meetings with patients group will increase confidence towards EMEA while quick alerts will be more effective in disseminating pharmacovigilance issues on the same population.

Overall, the representative groups agreed that EMEA runs the right actions to ensure appropriate communication. Many opinions even considered EMEA as a reference in this domain.

While we agree that EMEA uses the correct communication mechanisms, stakeholders’ opinions showed limited satisfaction regarding the communication effectiveness. The interviews suggested that healthcare professionals and general public are not aware enough of EMEA activities.

While some improvements could be monitored by EMEA itself (described above: languages, telematic projects), this contradiction is mainly the consequence of two factors:

- ▶ Almost all patients’ organisations do not have sufficient funding to convey EMEA messages to the concerned public. As it is pointed out in some patients’ organisations forum, communication is the area which is particularly suffering from the lack of funding. However, the EMEA cannot solve this issue within the scope of its activity. Still, EMEA intends to assess the channels of communication within a patients’ organisation before said organisation should get involved in EMEA activities (Doc. Ref. EMEA/333929/2005)

- ▶ While EMEA has a central role in monitoring the information related to public health, NCAs are still responsible for conducting the activities within their territories. It is perceived that some NCAs do not sufficiently convey the messages of the EMEA. Yet, the stakeholders (EMEA-NCAs-Public) are all elements of a communication chain. If one of the elements is not consistently providing the same message as the others, the communication has less impact on the public.

EMEA could increase its communication on the healthcare professionals and patients by increasing the visibility of the existing information monitored

Consequently, since the EMEA should obviously not act over the NCAs, the Agency could give the opportunity to healthcare professionals and patient groups to look directly to EMEA as a source of information.

To do so, rather than trying to communicate directly to the concerned stakeholders, the EMEA could increase its visibility by punctual communication actions in order to alert on the information already monitored on their website:

- ▶ Increase exposure through media and use of specific e-mail to organisations
- ▶ Monitor dedicated and practical guidelines to effectively use the existing communication mechanisms. In particular, it is imperative to increase the effectiveness of the communication by ensuring that existing information is known by the concerned stakeholders. For example, most members of the EMEA confessed that it's only after joining the EMEA that they got to know the benefit of some EMEA outputs for their day to day work, like for instance the EPARs. Similarly, leaflets could also be more focused on patients' understanding.
- ▶ Produce targeted communication: publication on scientific domains of interest for healthcare professionals, information of where a product is marketed for the public
- ▶ Design the website so that information is easily printable and allow easy copy-paste features (in particular for EPARs)
- ▶ Attempt to make all publications in all EU languages

5.4. Impacts on EU internal market

*To what extent has the EMEA contributed to an effectively operating **internal market** for human and veterinary medicinal products?*

Summary

EMEA contributes to the harmonisation of the EU internal market for medicines. As we have seen before, the Centralised Procedure, EMEA guidelines and EMEA post-authorisation activities all are major contributions to the harmonisation of procedures, and thus contribute to the harmonisation of market itself. EMEA impact on harmonising the EU internal market should however be further enhanced by EMEA ability to provide services to the industry as seamlessly as possible, as well as ensuring that such services are provided in a fair, cost-appropriate and transparent manner. In terms of pre-authorisation activities, scientific and regulatory advices should also contribute to enhancing the predictability of the outcome of EMEA evaluations for the industry. Finally, major steps have been taken by the Commission recently to improve support to SMEs and increase generic products entry on the market, which could greatly enhance EU market harmonisation. EMEA is actually adjusting to the consequences of such initiatives.

From the services point of view, **stakeholders generally recognize that EMEA continuously strives to improve both its timelines and its procedures.** Timelines are mostly respected for the centralised procedure, although the recent increase in workload may put such a performance at risk. The scientific advice, in contrast, is not reliable in terms of timelines, which is a major hindrance to the industry.

With regards to fee policy and practices:

- **The human pharmaceutical industry consider EMEA fees to be fair and appropriate to the evaluation work done with the notable exception of Scientific Advice** often considered too expensive. This may be linked on the one hand to the absence of engagement from the EMEA to accept results that follow scientific advice (thus decreasing predictability of outcomes) and on the other hand to the fact that many NCAs, provide scientific advice for free. Although CHMP/CVMP opinions may stray from Scientific Advice (given very early on during the product development) for very legitimate reasons, the lack of engagement remains an issue with the industry. This situation is probably enhanced by the implicit comparison that the industry always makes with the FDA, whose scientific advice is both free of charge and considered more binding, in part because it is compulsory.
- **The veterinary pharmaceutical industry is more dependent on EMEA fees rates**, as the centralised procedure may prove less attractive because of more fragmented and species-specific markets. Also, MUMS medicines do not benefit from the same incentives as Orphan medicines do, and this is a limitation to the improvement of veterinary medicines coverage.
- Independently of the fees level, **EMEA fee structure is complex**, as resulting from consecutives regulations. It may benefit from a simplification to lighten the administrative procedures.

Scientific and regulatory advices also are major tools that can contribute to increase the predictability of evaluation outcomes.

- **Scientific advice is considered helpful by all stakeholders**, and the steady increase of the number of applications to Scientific Advice is an indicator of this success. Industry representatives underline **Scientific Advice use and quality**, especially in helping them getting better prepared and providing the right data.
- The **recent introduction of a new procedure for Scientific Advice has been welcomed**, as it has helped reducing timelines and simplifying the process.
- However, **recent surveys conducted by EFPIA show that industrials tend to think that**

scientific advice is not as predictive of CHMP opinions as they would have expected. Moreover, the issue of scientific advice consistency with committees' opinions (PDCO and CHMP) has been raised, and should be treated with care, so as to avoid any contradiction that could damage medicinal development.

- It is also the case that both companies and NCAs have regretted the **high level of formalisation of Scientific Advice**, which may in certain situations hinder the discussion. However, such formalism may also prove a guarantee of independence and transparency.

EMA has recently put a lot of effort in order to improve its level of transparency, going beyond the legislation requirements. These efforts are recognized by the industry and other stakeholders. EMA is also already considered by NCAs as setting the example in terms of transparency. This commitment does not go without a higher level of resource needs, and should be further strengthened by the recent proposal for a consistent Transparency Policy for EMA.

The Commission and EMA support to the entry of generic medicine on the EU market, and in particular the introduction of generic medicinal products into the Centralised procedure, have proved extremely efficient.

- This has resulted in a **major increase of the number of centralised applications for generics, which now represent approximately half of the submissions.** The ability of CHMP to answer such an increase in workload is put in question, and the possible adjunction of a specific sub-committee responsible for generic application evaluation, while keeping the CHMP as the only committee issuing an opinion, is suggested.
- **On the veterinary medicinal products side, the introduction of generics has raised multiple issues.** First, as is the case for other veterinary medicinal products, veterinary generic medicines generally do not go through the centralised procedure, but rather through DCP or MRP. However, they raise an important amount of referrals, due mostly to the important variations in veterinary European medicinal products (variations in formulations, withdrawal periods, species indications, etc.).
- **Specific efforts for the harmonisation of veterinary European medicinal products should be implemented, in particular with regards to the anti-infective and anti-microbial products**, for which there are major risk of antimicrobial resistance emergence. Here again, there have been suggestions for a specific workforce dedicated to managing the necessary harmonisation before generic introduction, as well as ongoing referrals for generic. This workforce would report to CVMP, which would remain the only decision-maker.
- Moreover, **unnecessary delays and administrative procedures arise due to the obligation to re-assess eco-toxicity fully for veterinary medicinal products.** As such an assessment is compulsory for each equivalent reference product; it should not prove necessary to add such an additional evaluation, which both increases companies' administrative burden and CVMP workload.

5.4.1. EMEA contribution to reduce timelines and administrative burdens

As an industrial stakeholder neatly underlined in an interview, *“Companies expect from the EMEA that EMEA expectations are clear and well-defined, in terms of demands, process and timelines, that the evaluation is of high level and consistent and that there are predefined mechanisms to solve misunderstanding or tensions that may arise”*.

In this question, we will thus focus our attention on industry’s expectations in terms of cost, timelines, procedure simplicity and relationship with EMEA (the quality of scientific evaluation has been treated elsewhere). We will try to evaluate whether and how these expectations are met. To summarize, it may be said that industry stakeholders generally agree that EMEA fees are in accordance with the evaluation activities provided (with the notable exception of scientific advice), but still call for improvement regarding procedure simplification, which impacts both timelines and the formalism of their relationship with EMEA. However, industry stakeholders unanimously recognize EMEA efforts and recent improvements in terms of decreasing administrative burdens and constantly seeking to simplify and shorten procedures. They also unanimously underline the positive interaction that they entertain with EMEA Secretariat and their impression of being generally heard, except on very specific cases (see for instance guidelines).

EMEA fees structure is complex

First of all, and independent of the level of fees, it must be noted that EMEA fees structure is relatively complex, which necessarily adds to the administrative burden of industrials dealing with it.

Application for marketing authorisation is split between a basic fee (covering a single strength associated with one pharmaceutical form and one presentation) and two types of additional fees.

In the same way, a basic fee and an additional fee apply to extension for marketing authorisation, with the basic fee covering one extension and the additional fee covering each additional presentation of the same extension submitted at the time of the extension application. European legislation also distinguishes between two types of variations

- Minor variations i.e. Type Ia and Ib,
- Major variation, i.e. Type II.

All types of variations are submitted to a basic fee.

EMEA also gets fees for renewal of marketing authorisation, inspections, transfer of marketing authorisation, maintenance of a marketing authorisation (annual fee), referrals initiated by the MAH (Article 30(1) and 31 of Directive 2001/83/EC), Scientific Advice, Scientific Services (also working with basic and additional fees) and Consultation on ancillary substances.

An additional layer of complexity is added by the multiple fee reductions that apply to some of these services, with various levels depending on the type of applicant for a reduction (generic product, biosimilar product, product for paediatric use, advanced therapy medicinal product, orphan medicine, immunological products for veterinary use and SME applicants).

In comparison, it is noteworthy that FDA fee structure is limited to only 5 types of fees in the following categories: application requiring clinical data (roughly equivalent to EMEA initial application), supplement requiring clinical data (roughly equivalent to an extension or a Type II variation), application not requiring clinical data (roughly equivalent to a generics/biosimilar application), product (equivalent to annual fee), and establishments (no equivalent). Although European legislation distinctions are legitimate and probably provide a fairer set of fees, one could argue that a simplified ratemaking may facilitate EMEA operations and alleviate industry’s administrative burden.

Recommendations regarding fees:

- EMEA could provide support to industrials in navigating its fee system by helping them estimate, through a multi-choice web interface, the applicable fee for a given applicant in a given situation
- The Commission and EMEA could work jointly on a simplification of EMEA fee structure, while keeping the fairness of fees as an important goal. The fees will be subject of a report on the Implementation of the Fees Regulation which the Commission is to submit to the Council by 24 November 2010 (Article 12 of the Council Regulation (EC) no 297/95 on fees payable to the European Medicines Agency). Following this report, the Fees Regulation is expected to be reviewed. This potential reorganisation of fee structure should also consider the sustainability of both EMEA and EMEA stakeholders' involvement, as well as the appropriate level of compensation asked from the industry.

EMEA fees are generally considered appropriate, although human and veterinary sectors may give divergent feedbacks

In terms of fees, feedback varies mostly as a result of the type of company (veterinary-focused or human-focused).

Companies producing human medicinal products recognize the economic interest of the Centralised Procedure, both in terms of simplification of procedures (see 1.1.1) and of cost. Both companies producing innovative drugs and companies producing generic medicines share this opinion. Indeed, a DCP for human medicinal products may cost an applicant as much as €1 million if the companies goes through submitting applications on the main markets, while a centralised procedure's basic fee was 251 600€ in 2009.⁴⁴

An interesting comparison is given by FDA fees, though the comparison seems not perfectly fair since procedures and classifications differ between the two agencies (EMEA and FDA). Interestingly, and notwithstanding these important differences, most stakeholders consider that both agencies end up giving very high quality to excellent evaluations. It is important to note beforehand that the European pharmaceutical market size is equivalent to roughly 2/3 of the US one.⁴⁵

EMEA basic fee rates for initial application for marketing authorisation are largely in line with FDA ones (see Table 5). The EMEA fee structure seems more complex than the FDA fee structure: there are specific cases for 3 different types of variation (Type Ia, Ib, II) beyond extension, additional fees for specific strengths or presentations, as well as referral fees. There are also more cases for reduced fees or waivers, targeting generics, biosimilars, orphan and paediatric products, as well as small and medium enterprises (see part 5.4.2). On the other hand, some of the fees asked by FDA do not exist in the European system, for instance the establishment fees (US\$457 200 a year for each establishment that manufactures an authorised product, although this fee may be split between different applicants using the same establishment for production). Also, FDA applies some waivers and fee exemptions in specific cases.⁴⁶

⁴⁴ This is an estimate given by multiple interviewees, not necessarily covering the 27 EU countries.

⁴⁵ European Population is estimated to reach 499,8 million people in 2009, vs. 307,7 million people in the USA. From the global pharmaceutical sales for human medicines of US\$634.7bn in 2007, US sales were estimated to US\$ 278 bn, whereas the 5 major EU markets (Germany, France, UK, Italy and Spain, equivalent to 63% of EU population) only represented US\$ 137 bn. European sales growth, however, is higher than US sales growth (Source: IMS Health, 2008).

⁴⁶ Exception to FDA fee requirements include exceptions for applications fees for previously filed applications or supplements, exemption for application fee for designated orphan drug or indication (both for a prescription drug product or for a supplement),

EMEA Centralised Procedure		FDA rates (2010)	
Basic Fee for initial application ⁴⁷	251 600 €	Application fee with clinical data	1 405 000 US\$ (~955 400€) ⁴⁸
Additional fees	For additional strengths or pharmaceutical forms or presentation		
Reduced Additional Fees	For generics and biosimilars		
Extension or Type II variation	75 500€	Supplement requiring clinical data	702 750 US\$ (~477 870€)
Applications for a MA pursuant to articles 10(1), 10(3) and 10c of Dir. 2001/83/EC as amended.) (<i>Mostly generics</i>)	97 600 €	Application without clinical data (<i>Mostly generics</i>)	702 750 US\$ (~477 870€)
Annual fee	90 200 €	Annual Product Fee	77 720 US\$ (~52 850€)
Reduced annual fees	45 100 € for biosimilar medicinal products 22 500 € for generic medicinal products	No waiver on Product Fee	-
		Establishment Fees	457 200 US\$ (~310 896 €)

Table 5: Comparison of fees rates between FDA and EMEA⁴⁹

Sources: Federal Register Vol. 74 N°147 for FDA rates, Explanatory Notes on Fees payable to the EMEA, EMEA/199262/2009 for EMEA fees

For the comparison, we were able to roughly model the cost for an innovative product that does not benefit from any reductions and for which the applicant does not seek any additional presentation,

exceptions for establishment fees when the establishment does not produce the product during a given fiscal year, and exceptions for product fees Waivers and reduction are applied in the following cases when it is necessary to protect public health, whenever the assessment of the user fees would present a significant barrier to innovation due to limited resources or other circumstances, and whenever the fees are considered as exceeding the anticipated present and future costs incurred by FDA for conducting the process for the review of the new drug application.

⁴⁷ Basic and additional fee also exist in « reduced » versions for generics and biosimilars.

⁴⁸ All figures are given using an exchange rate of 1\$=0,68€ (Oct 2009 exchange rate). Of course, the figures of the comparison may change in case the exchange rate changes.

⁴⁹ Please note that comparison has included as much as possible fees that cover similar services. However, it is important to keep in mind that classifications are not exactly similar between both agencies and that specific reductions and waivers apply in both agencies.

strength, indication or variation. A product is generally on the market for 10 years, before it reaches the generic status. During this period, the costs for marketing authorisation in USA amount approximately to €1,48 million (not including establishment fees, which may vary), while the costs for marketing authorisation in the 27 EU countries amount to approximately €1,16 million (not including referrals or inspection fees, which may also vary, but including one renewal of marketing authorisation, which costs 12,5k€). Although, as we said before, the EU market is smaller than the US one, fees thus seem to be relatively coherent for a given product on its marketing authorisation period as an ethical medicine.

Generics, on the other hand, inasmuch as our example is valid, would benefit from a much better situation in the EU than in the USA in terms of fees for marketing authorisation (approx. €1 million for a 10 years period in the USA vs. 322 200€ in the EU).

It is noteworthy that the European legislation states that EMEA offers significant fee reduction and exemptions for SMEs, as well as for orphan medicines and paediatric medicinal products. These waivers and reduction are considered extremely important by all stakeholders in order to maintain innovation.

Orphan medicines, paediatric medicinal products and advanced therapies have been discussed elsewhere (see the part about the impact on citizens). However, it is also important that legislation states that EMEA offers specific fee incentives to promote their development (see Table 6). Although all companies approve such incentives, they create a challenge in relation to the system's sustainability and efficiency (see 5.2.1).

Type of products	EMEA Service	Type of applicants	Reduction
Orphan medicines	Protocol assistance	All	100% fee reduction to the total applicable fee
	Inspection (pre-authorisation)	All	100% fee reduction to the total applicable fee
	Application for Marketing authorisation	All except SMEs ⁵⁰	50% fee reduction to the total applicable fee
Medicinal products for paediatric use	Application for marketing authorisation	All	50% fee reduction to the total applicable fee
	Inspection (pre-authorisation)	All	50% fee reduction to the total applicable fee
	In the first year after MA: Extension to a MA, Variations, Annual fee, Inspection (post-authorisation)	All	50% fee reduction to the total applicable fee
Advanced Therapy medicinal products	Scientific advice	All except SMEs and hospitals ⁵⁰	65% fee reduction to the total applicable fee

Table 6: Fee incentives and exemptions relative to orphan medicines, medicinal products for paediatric use and advanced therapy medicinal products under the current European legislation⁵¹

Source: Explanatory Note on Fees payable to the EMEA, EMEA/199262/2009

⁵⁰ Specific fee incentives for SMEs are presented in Table 7. Incentives for advanced therapy medicinal products intended for hospitals and relative to products already on the market in accordance with national or Community legislation on 30 December 2008 are not presented.

⁵¹ As described in the report earlier, there also exist incentives for MUMS products in the veterinary sector

To summarize, fees for human products are generally considered appropriate by the industry, which tends to think they compare favourably with other regulatory agencies. The most notable exception is fees for scientific advice (75 500€⁵² for an initial request), which are unanimously considered too expensive (see below). The fact that many NCAs provide scientific advices free of charge may play a role in this opinion. Even though the FDA's scientific advice is compulsory and part of the global evaluation process, the perception of the industry is that it is free of charge, which further reinforces the opinion that EMEA scientific advice should be less expensive.

Some stakeholders also raised the issue of “paying twice” for duplicated applications (e.g. two trade names for similar products in two different countries because of different patent status). This is of course of particular relevance to the generic industry. However, the recent significant reduction of fee for duplicate applications as a consequence of a national usage patent in the reference product was welcomed. Moreover, the undergoing work on patent protection harmonisation should in the end reduce this issue. Industry representatives have also underlined the fact that EMEA has taken measures to improve the dialogue with them on all naming issues⁵³.

For veterinary medicinal products however, the situation of fees differs significantly, as many products do not justify an application in all 27 markets at the same time (see the answer to the first evaluation question). Indeed, in many situations, it may prove less expensive to choose the decentralised procedure, even though the veterinary fee is already 50% less than the human one (but the procedure for evaluation remains the same and thus generally involves the same number of staff both at the EMEA and the NCA level). It is interesting to note that, contrary to the situation encountered with human medicinal products, FDA initial application fee for marketing authorisation is a little cheaper than EMEA one (125 800€ for EMEA, which is already discounted relative to the human fee, vs. US\$ 172 500 for FDA, i.e. 117 300€), while the US market still is bigger than the European one. This adds weight to the request often formulated by veterinary industrials to reconsider EMEA fees. Veterinary industry representatives argue that the veterinary market is much smaller than the human one and that their investment in R&D is already difficult to compensate independently of regulatory expenses. From the EMEA point of view, however, veterinary resources represent 10% of the staff while generating only 5% of its revenue, due to the wide range of activities and skills to cover (which are equivalent in diversity to human activities, without taking into account the MRLs assessments). Thus, a reflexion could be launched on the ability of EMEA to reconsider its fees towards the veterinary industry while keeping the appropriate level of staff to perform evaluation.

EMEA timelines have improved but there is still space for simplification of procedures

Timelines are of utmost importance to the pharmaceutical industry. Indeed, a delay to reach the market may be extremely costly, both for innovative and generic medicinal products. Since medicine development is a very long process, often spanning on more than 10 years, companies tend to try to plan as precisely as they can to avoid any additional delay. Thus, timing is of importance not only at the evaluation level, but also in all other pre-authorisation services that EMEA may provide the industry. Even more than the absolute time spent on an activity, it is its predictability that matters to the industry.

As mentioned earlier, one of the key success factors for the centralised procedure is that it is more predictable in terms of timelines than the MRP or DCP. Since 2000, EMEA has always respected the regulatory timeline of 210 days for the assessment phase (see Figure 65). With the exception of 2004, the decision process phase managed by the European Commission after provision of EMEA opinion has

⁵² This is the basic fee for an initial request for scientific advice on quality and safety and clinical development, or quality and clinical development or safety and clinical development or qualification advice.

⁵³ On the related subject of naming policy, see EMEA – EFPIA Info Day 2009 reports on Naming Policy by Zaide Frias (EMEA) and Anja Manz (Novartis Pharma).

regularly decreased in duration since 2000, from 92 days in 2000 to 29 in 2006. In general, the best performance in terms of timelines was achieved in 2006. It is important to note that the recent increase in workload has not yet impacted significantly EMEA ability to respect the legal timelines. However, timelines have tended to increase slightly again since 2006. 210 days seem appropriate to most industry interviewees, who seem to understand that shortening timelines may impact the quality of the evaluation if this is not accompanied by an increase in evaluation resources or a change in the organisation of CHMP to manage an ever-increasing workload. Some NCAs have complained that 210 days sometimes proves too short, which seems to be confirmed by the augmentation of demands for additional time for evaluation after a negative opinion. It is clearly the case that dossiers for innovative products take more time and resources to investigate. As some NCAs pointed out, dossiers where some data has already been investigated elsewhere (including generics or products that have already been authorised in another country for the MRP), are much faster to manage. Thus, if generics benefitted from a specific procedure for generics and a subcommittee to the CHMP, this could probably improve timelines both for generics and for other products, by decreasing CHMP workload and freeing resources to perform evaluation.

On average on the 2000-2008 period, the duration of an evaluation was 440 days, including the company clock-stop time. This duration sometimes raise some concerns among stakeholders. During that period, company clock-stop time tended to increase before 2004, and decrease again after that date. Indeed, most interviewed companies noted that important improvements in the evaluation procedure (including the clarification of the list of questions), made it easier for them to answer in a shorter period of time. Smaller companies also underline the importance of guidelines and other support services in improving their level of preparation and thus decreasing time spent on clock-stop activities.

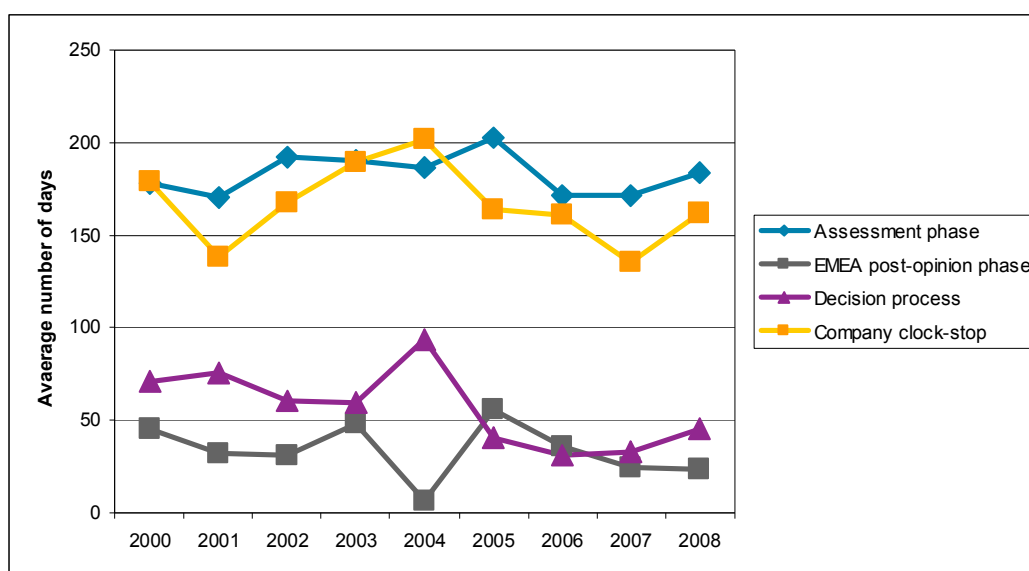


Figure 65: Average number of days spent on initial evaluation (for positive opinions only). Source: Annual reports 2000-2008

Source: EMEA annual reports (2000, 2001, 2002, 2003, 2004, 2005, 2006, 2007, and 2008)

In conclusion, any improvement in evaluation timelines would probably be minor, due to the need for a minimal time for an evaluation of quality.

However, numerous stakeholders have complained that EMEA is not as reliable in its timing for scientific advice as it is for evaluation (see below). A clarified process for scientific advice, including precise timelines for answering, may thus prove beneficial.

Industrials also insist that, beyond EMEA evaluation, there are additional delays that may lengthen the time-to-market. In particular, one such delay is due to the translation of SPCs in all European languages.

In that regard, additional support may be sought for. Another such delay is linked to the good will of countries to enforce EMEA decision in due time.

EMEA formalisation is sometimes a hindrance to good communication and relationships with the industry

Some specific points were raised during this evaluation regarding the formalisation of EMEA procedures, as well as other aspects of the industry's relationship with EMEA.

A general comment that was made regarding a few of EMEA activities (including Scientific Advice, Hearings, or Pharmacovigilance) was the strong tendency of the Agency to make contacts more formal than may be necessary. Such comments were generally not made concerning the relationships between PTLs and industry project leaders, although it was sometimes regretted that the direct link between the applicant and its Rapporteur and Co-rapporteur had been recently severed. For instance, many industry representatives regret that the only situation when they have the opportunity to directly enter in contact with CVMP or CHMP is when they ask for a hearing. They also think that the formalisation of EMEA scientific advice (written responses only), does not facilitate their understanding of the issues raised.

Clearly, requests for a more informal communication get in the way of a strict policy for transparency, and the need for formalisation has increased with the EU enlargement. However, most NCAs insist that they manage to keep independent while allowing a more continuous and informal dialogue with the industry. There is a clear concern at the industry level that EMEA is getting to be more and more bureaucratic and that some recent evolutions, including the focus on transparency, may strengthen this tendency.

Another important issue is the independence of the appeal Procedure⁵⁴. Many stakeholders, both from the industry and the assessment sides, have expressed their concern regarding the fact that referrals are formally treated by the same Committee that has expressed a negative opinion before. Although Rapporteurs and Co-Rapporteurs usually changed, the same committee remains competent. It is unclear, however, what kind of measure could be taken to answer this problem. Indeed, the very legitimacy of the Committees is ensured by the presence of all Member States' representatives, many of which could not be replaced easily to form a second judging committee.

Other major administrative burdens include Pharmacovigilance and the impact of the recent Paediatric regulation. Both have been treated in previous parts of the report.

⁵⁴ This applies to all referral procedures, whatever their source.

5.4.2. Contribution to the harmonisation of European Marketing Procedures

EMEA aims at contributing to the harmonisation of European Marketing Procedures. To reach such a goal, EMEA must facilitate harmonisation of the evaluation procedures per se, but also of post-authorisation as well as pre-authorisation activities. Thus, the centralised procedure, scientific advice and guidelines all contribute to harmonisation. Moreover, harmonisation is only strengthened by EMEA ability to make sure its decisions are fair and well understood, by using transparency policies. At the very end, not only decisions must be harmonised but also their implementation. This is why the ability of EMEA or the Commission to check that issued decisions are binding to Member States also contributes to harmonisation. We will consider each of these points in the following paragraph.

As we discussed earlier, the Centralised Procedure importantly contributes to harmonisation of practices and evaluation across Europe, although some specific points still need to be improved (in particular consistency over opinions given at different times or by different committees). We also showed that guidelines prove extremely important in helping both companies and assessors to adapt to the legislation in a coherent way, and in making the evaluation more reproducible and reliable across European countries, both for the centralised, mutual recognition and decentralised procedures. (see the part on the contribution of guidelines).

Beyond evaluation per se, EMEA, also contributes to harmonisation by helping companies understand and anticipate evaluations through scientific advice.

Scientific Advice: positive outcomes and increasing activity, although minor improvements may be needed

Scientific advice is generally acknowledged as being of very good quality and as facilitating the capacity of companies to adapt to European regulatory requisites. Stakeholders underline that EMEA generally has access to the right experts to deliver scientific advice (both from the 30 members of the SAWP members and through external experts), although some difficulties may arise for very specific conditions or topics. This is confirmed by the very positive outcome of EFPIA Survey on Scientific advice published in 2008⁵⁵.

The introduction of a new procedure for scientific advice in 2006 has shortened the process, with procedure being carried out between 40 to 70 days (vs. 100-day procedures before). The principle of publishing frequently asked Questions-and-Answers also is considered an advantage, and beneficial to the overall harmonisation of development plans.

EMEA scientific advice success can be measured by the constant increase of submitted and finalised requests for human medicinal products since 2001: for instance, the number of received scientific advice requests increased on average 26% a year during the 2001-2008 period (which means a total increase of 471% in requests, see Figure 66). For comparison, in 2008 the number of received scientific-advice and follow-up requests (264) was more than twice the number of centralised procedure applications (103). Protocol assistance requests, on the other hand, tend to stabilise since 2005, which may show that the centralised procedure is now well known and managed by most applicants.

⁵⁵ EFPIA conducted a survey of users of the novel procedure for Scientific Advice between July 1st 2006 and June 30th 2007. The survey contained 81 questions that covered all stages of the scientific advice process and got responses from 78 companies. It was published on June 2008.

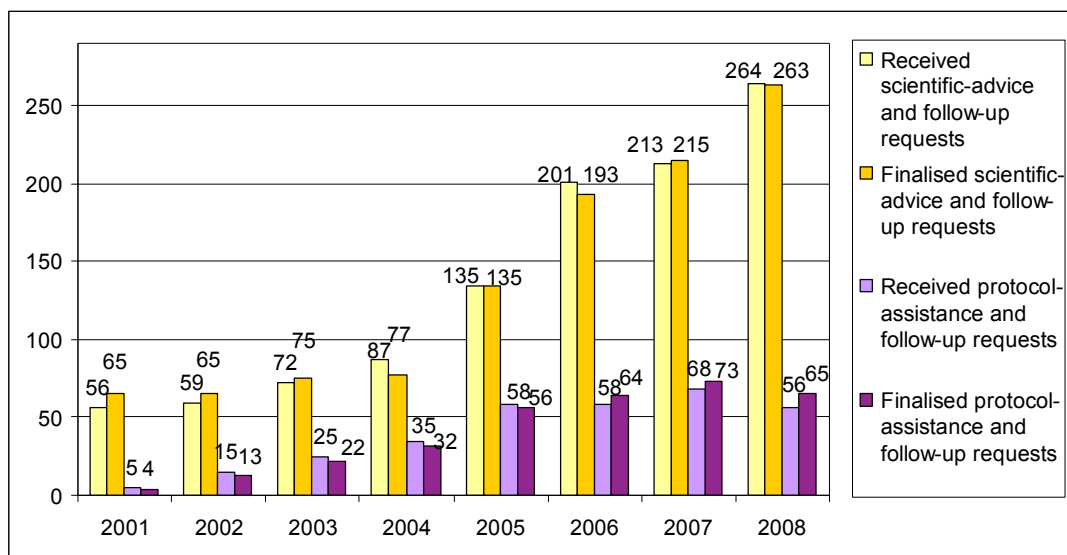


Figure 66: Evolution of the number of received and finalised scientific advice and protocol assistance requests for human medicinal products from 2001 to 2008

Source: EMEA Annual Reports 2001-2008)

As shown in Figure 67, the veterinary pharmaceutical industry does not apply as much for scientific advice as the human pharmaceutical industry, and although there was a global increase in requests numbers during the 2001-2006 period, the number of requests has tended to decrease since 2006. In 2008, there were only 5 requests, as compared to 16 applications for the centralised procedure.

This relative lack of interest for scientific advice in the veterinary sector may be the result of various factors. First, some innovation on the veterinary market may be derived from the human sector, thus not requiring renewed scientific advice. More importantly, veterinary industrials suggest that the price for scientific advice is quite high relative to their margins, which are smaller than in the human sector. They also tend to rely more on the national scientific advice, which they consider less formal and of nearly equal quality in active agencies. Moreover, national scientific advice is often free of charge.

Regarding veterinary medicinal products, some interviewees have also suggested that emphasis could be put on helping companies deal with MRLs applications, by providing specific advisory support on this topic. In that case, the Secretariat could probably play a greater role, since its expertise on MRLs is widely recognised.

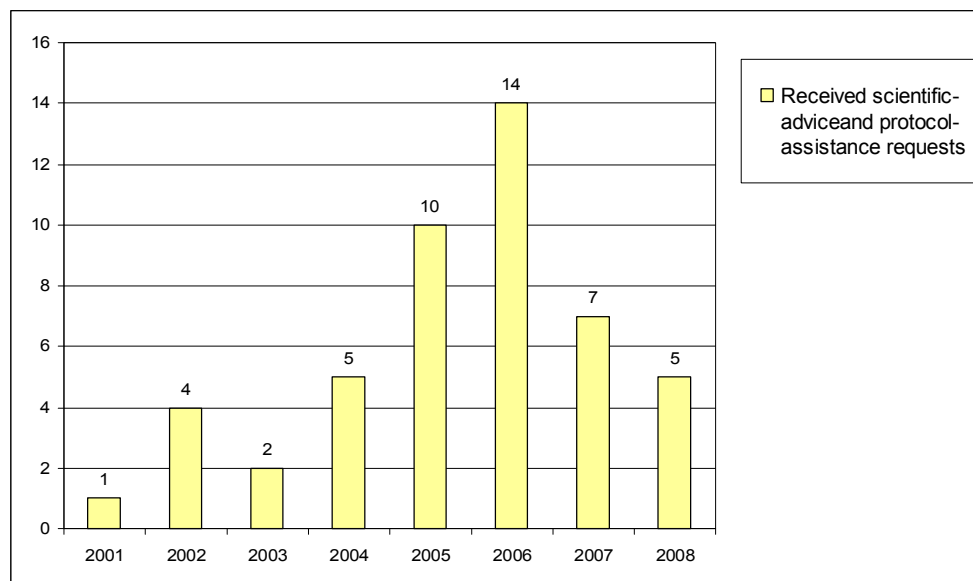


Figure 67: Evolution of the number of received scientific-advice and protocol assistance requests for veterinary medicinal products from 2001 to 2008

Source: EMEA Annual Reports 2001-2008)

Scientific and regulatory advices are overall recognised for their quality, and they definitely improve companies' preparation. Most industry stakeholders have underlined that it is of high importance to ensure that the company will make the right application, containing the right type of evidence and thus preventing possible wastage in R&D.

Moreover, scientific advice, pre-submission and negotiation meetings often prove more fruitful than hearings done in appeal of centralised procedure negative opinions, partly because scientific advice meetings are more informal and partly because they happen earlier in the process, when much can still be done to improve the outcome.

It is important to note that the generic industry also think scientific advice is useful for the development of biosimilars. Quite understandably, scientific advice is of lesser relevance for other generic medicinal products, for which the process is very straightforward and is also considered less formal, prompting more open discussions than is the case for other applications.

However relevant scientific advice may be, some difficulties have been reported. The main complaints were that the timelines are quite long and not reliable, the price may prove high for some companies, and the formalisation of the procedure may prevent in-depths discussions. The creation of new committees with advisory responsibilities also worries the industry as potentially providing space for incoherence between CHMP Scientific advice and other committees' (especially PDCO's) advice.

Timelines have improved, but remain unreliable

Although they consider Scientific Advice to be very useful and of very good value, industry representatives often regret that the process is too complicated and thus takes too much time, especially when compared to scientific advices at the national level or in the USA. More important, the timelines may largely vary, and this is a critical limitation for pharmaceutical products development, for which timelines matter so much. Some of the largest companies even suggest that the fees would not be a problem if the timelines were assured. However, it is noteworthy that the new procedure, implemented since 2006, already brought significant improvements in terms of timelines (see EFPIA Regulatory Survey 2008). At this stage, the main point for improvement of procedure would be the pre-submission phase, since a pre-submission meeting may increase the process duration by one month. This may be the reason why it is less used than other services.

EMEA formalisation with regards to Scientific Advice may occasionally hinder fruitful discussions

EMEA Scientific Advice was unanimously reported as more formal than the NCAs' Scientific advices, as well as the FDA scientific advice. In particular, SAWP only provides written responses. While this formalisation is understood to be a consequence of having 30 countries present at the table, some observers nonetheless believe that it may hinder a more open discussion between the applicant and its advisors. At the national level, some NCAs avoid giving written responses and rather favour face-to-face meetings.

In this respect, it is also interesting to note that some companies believe it useful to ask for both European and national scientific advices, as they do not provide exactly the same type of information. EMEA Scientific Advice is sought because it ensures a good level of security regarding the development of the product, while NCAs are more concerned with local access for the upcoming medicine, and also provide a less formal and faster response.

Sweden: scientific advice

At MPA, the industry can send in questions, which are debated by an internal team within MPA. Then 3-4 MPA people, having decided their position in advance, meet directly with the industry in an informal way. Although MPA scientific advice is not legally binding, the whole MPA team is understood to speak as MPA representatives. At the EMEA, there is no internal pre-meeting, and whoever speaks is not directly understood to speak for the EMEA in a binding way. The meeting itself is much more formal, with about 15 people facing the industry. There still is an option for the company to ask for follow-ups to scientific advices, which may be less formal, but it is not a straightforward process.

Scientific Advice is a successful procedure as it stands, but may benefit from :

- Streamlining the pre-submission process
- Facilitating communication with the industry, maybe by making an entry point more available throughout the procedure (and not providing only written responses)
- Launching a reflexion on fees, especially for Veterinary products
- Launching a reflexion on the sustainability of the system to adjust to increased workload, and ways to solicit new resources
- Pursuing the already begun facilitation of communication between SAWP, PDCO, CHMP and related sectors at the Secretariat, so as to avoid any misinterpretation, loss of data or incoherence.

Scientific Advice Fees are considered high by the industry, while NCAs ask for a better compensation

Some industrials regret the level of fees for Scientific Advice, especially middle pharma and biotechs which can not benefit from the SMEs' advantages but still have to consider carefully the costs incurred during development. In particular, some interviewees reported often dropping the idea of getting scientific advice when considering the cost. It is even more salient that FDA scientific advice is perceived as free, although it is compulsory to apply (and as such compensated through the general fee for application) and some NCAs also provide free scientific advice. This also raises the question of the sustainability of the system, since the workload has constantly increased for human products in recent years and the resources available for NCAs do not necessarily follow this rate. Some NCAs also raised the point that the lack of compensation may lead to a lack of resources, especially in the veterinary sector where they are scarcer.

Current challenges and risks

The recent creation of the PDCO, which in a sense provides specific scientific advice for the development of paediatric products, has created the concern amongst stakeholders that its opinions may contradict those of the SAWP. Indeed, in the beginning of its operations, there have been reports of contradictory opinions emerging from SAWP and PDCO. The fact that some members attend both the CHMP and PDCO does not seem to be enough to counter this risk, especially since members' schedule is very tight, and not all manage to really attend both meetings. This is a problem since following PDCO's opinions is mandatory for the industry, but CHMP may not agree with PDCO or even blame the company for not following SAWP's advice, if PDCO's and SAWP's advices differ.

To support this worry, a recent survey from EFPIA showed that companies considered that CHMP opinions are not very compliant with Scientific Advice (see Figure 68) and that perception seems to worsen over the years⁵⁶. If CHMP and SAWP are perceived to be incoherent in their opinions, the risk of incoherence with a distinct decision-maker committee, as PDCO, seems even greater.

This more generally raises the subject of the impact of Scientific Advice, as SAWP opinions are not currently considered binding for the EMEA (and thus they are not considered legally predictive of CHMP opinions⁵⁷). Indeed, some stakeholders also complained that they may have significant difficulties in justifying straying from EMEA scientific advice, while the CHMP would not need to justify itself when doing the same. The predictability of CHMP's opinions in relation with EMEA Scientific Advice would certainly benefit from further clarifications.

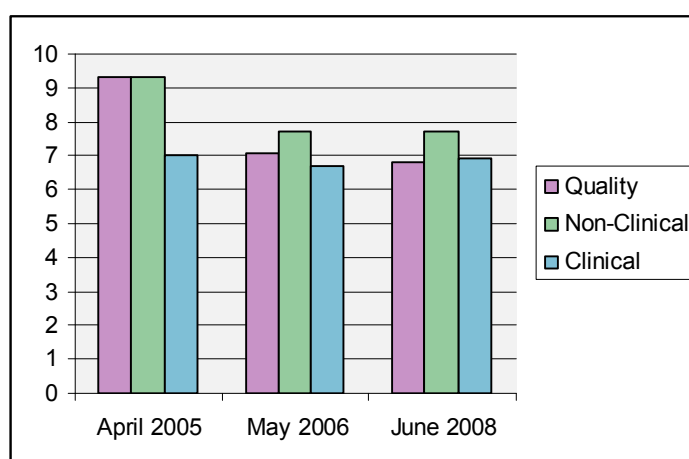


Figure 68: Perception of consistence of CHMP opinions with Scientific advice as measured by EFPIA surveys (2005-2008). The respondents were to rate on a 1-10 scale (10 being perfectly compliant).

Source: Perception Source: EMEA-EFPIA Infodays 2009, Pr. Jefferys' presentation

It seems, however that these difficulties are being taken into account. Efforts are currently being made to improve PDCO-SAWP communication, as well as enhancing the Secretariat's role in ensuring coherence between the various bodies' opinions. This last part is made easier by the fact that the same Secretariat Sector is in charge of paediatric affairs and scientific advice.

The coherence between PDCO, SAWP and CHMP opinions also raises the question of continuity of management of the product inside EMEA. As EMEA scientific advice is not binding, and different people may end up evaluating the product at various stages of its development, there may be issues of understanding and communication between the applicants and EMEA. The current reorganisation of the Secretariat may however answer some of these concerns, by putting in place a more streamlined

⁵⁶ David Jeffery, EMEA-EFPIA Infodays 2009

⁵⁷ Contrary to the FDA situation, where Scientific Advice is compulsory, but also binding to FDA.

process and attributing to a given product a common PTL for pre- and post-submissions activities. At this point, however, these suggestions have yet to be implemented. More generally, 2008 EFPIA Survey suggested that transparency could be improved in some aspects of the process, in particular by providing early information to the applicant on which coordinators are chosen, and whether they are from the SAWMP or external experts.

Industrials do not think that Scientific Advice should be made compulsory

Although they recognize the use of Scientific Advice, industry representatives have not asked for it to be compulsory: they consider having this option is beneficial, but should not be imposed on the product development plans. In particular, even though most stakeholders consider scientific advice to be very advisable for innovative products, they do not think it is necessary for generics, or more “regular” products. However, to ensure harmonisation of evaluation, assessors are supposed to know about previous scientific advice for a given class of product, and justify if they disagree on specific points.

EMEA already stands as an example in terms of transparency, although more efforts are expected. Resources considerations should however be kept in mind when implementing new procedures

EMEA has recently submitted to consultation a draft for a Transparency Policy⁵⁸. Consultation was closed on September 25th 2009 and EMEA is currently processing its outcomes.

The rationale for the implementation of such a policy is that, although EMEA already engaged in multiple ways to improve transparency in its operation, in accordance and beyond existing legislation⁵⁹, such initiatives have not been reconciled into a single policy that would ensure a more robust and consistent approach. It is also the case that EMEA has received increasing demands from all stakeholders (industry, patients and health care providers alike) to enhance transparency at various levels, including decision process.

It is already the case that most stakeholders recognize that EMEA already stands as an example in terms of transparency, and that recent efforts in this regard have proved extremely fruitful. Transparency is a key issue for the industry, as it supports both a fair competition and the predictability of the outcome of an application. It is also of importance to patients’ organisation and healthcare providers, in that it allows a better understanding of EMEA activities and rationale for taking decisions and emitting opinions. However, at this point, these stakeholders probably are the one with the lower impression of EMEA as a transparent body. From the NCA’s point of view, however, EMEA already sets the example for transparency rules, and most claim that they try to apply the same standards when doing evaluation for decentralised, mutual recognition or national procedures. Applying transparency rules means that more things have to be written and published, leading to important resource needs. It is generally thought that for the centralised procedure, the Secretariat plays a major role in making sure that transparency rules are being followed. Recent transparency rules nonetheless have increased the administrative burden weighing on NCAs acting as Rapporteur and Co-rapporteur. Moreover, NCAs generally do not have the appropriate level of resource to involve in transparency for other evaluation procedures, which may be the limit of harmonisation in this regard.

Recent steps taken towards more transparency include the creation of European Public Assessment Reports (EPARs), following Article 13(3) Regulation (EC) No 726/2004. EPARs are considered a major

⁵⁸ “The EMEA Transparency Policy, Draft for Public Consultation », London, 19 June 2009. Doc Ref EMEA/232037/2009 – rev.

⁵⁹ In particular, Regulation (EC) No 726/2004 laid the basis for specific transparency measures in EMEA activities, including the creation of EPARs (Article 13(3)). However, EMEA itself has also implemented numerous steps towards transparency and the Management board has documents related to this topic: EMEA/MB/053/00 (Report to the Management Board on the workshop “A clear step forward: transparency at the EMEA”); EMEA/MB/52/03/Rev1/Final (New EMEA Transparency Policy measures).

improvement and an important source of information for industrials, which also use them as a tool to improve competition.

Beyond the legislation requirements, the authorisation process for the centralised procedure is also considered fairly transparent by the industry, although this may depend on the Rapporteur. Indeed, some interviewees underlined that the introduction of Peer-Reviewing has increased the level of transparency, and prompts some Rapporteurs to be more explicit in their reasoning. The recent efforts towards the improvement of consistency, where the Secretariat plays an important role, are also recognized.

Some interviewees have also mentioned their expectation of better transparency regarding Paediatric Investigation Plans (PIPs) evaluation. For instance, applicants receive opinions from both the Rapporteur and Peer-reviewer, which may be divergent. Beyond these opinions, applicants generally want to know more about the reasoning that leads to the final decision. Regarding PIPs, another transparency issue relates to the publication of PIPs, which, from the industry point of view, may prove a danger to product development, releasing confidential information that competitors may use to their advantage. Multiple discussions are undergoing between EMEA and industrials to set the appropriate balance between transparency and confidentiality in this situation.

The current draft for an EMEA Transparency Policy strives to improve transparency by attaining three objectives: to apply a more proactive approach towards transparency in the daily operation of the EMEA (both at the Agency and the NCAs level), to further strengthen interaction with EMEA stakeholders and to enhance and promote closer interaction with the NCAs within the frame of the EU Regulatory System Network on transparency related aspects.

As we have seen, implementing such a policy should raise three major issues:

- The issue of resources needed to produce the necessary publications to make the process more transparent, both at the Agency and NCAs level;
- The issue of finding the right balance between transparency and fair competition, while keeping in mind the best interest of patients and citizens;
- The issue of keeping transparency requirements within the limits of existing national legislation on freedom of information, while striving for a more harmonised European system.

EMEA efforts towards a more transparent decision process should thus be encouraged, but whenever possible, specific efforts should be made in avoiding unnecessary administrative formalisation. EMEA could also be involved in more training activities towards NCAs, both to increase harmonisation of working procedures and familiarity with transparency rules. Rapporteurs, co-Rapporteurs and Peer-reviewers should be encouraged to write their opinions in the most explicit way. Secretariat should check that Committees' final opinions are consistent with previous opinions. If they fail to Committees should be able to publicly justify such a divergence.

EMEA intention of improving interaction with all its stakeholders seems of importance, as patients' organisations in particular are striving for a more transparent and understandable system, to compensate for a regulatory framework that is generally perceived as complex. This should go together with the improvement of EMEA communication policy (see the part about the impact on citizens)

Finally, harmonisation cannot be complete if Member States fail in any way to apply the Commission Decisions after EMEA has issued an opinion. Indeed, EMEA is not a decision-maker, but can only issue opinions that the Commission may or may not follow. EMEA lack of power in terms of making sure that its opinions are followed by Member States (once the Commission published a decision) has been raised by multiple stakeholders, including industry and patients organisations.

National procedures, after the EMEA opinion has been issued (effective delivery of authorisation, pricing and reimbursement procedures, specific naming requirements, etc.), may sometimes delay the actual time of access to market for some medicines, although this is considered to have improved in the last 3-4 years. It is also the case that when EMEA gives recommendations, it has no way to encourage the NCAs to implement them. For instance, CVMP has recently worked on fluoroquinolones, and issued a recommendation to modify all SPCs for quinolones and fluoroquinolones for safety reasons and to avoid

unnecessary referrals procedures. A follow-on questionnaire showed that only half of the NCAs did modify the SPCs.

Thus, either the Commission or EMEA power to control for timely application of Commission’s decisions should be enhanced.

5.4.3. EMEA supports SMEs and their ability to innovate

EMEA activities and incentives towards SMEs have met success

On 15 December 2005, the EMEA launched an SME Office to provide financial and administrative assistance to micro, small and medium-sized enterprises (SMEs), with the aim of promoting innovation and the development of new human and veterinary medicinal products by these smaller companies.

Enterprises with less than 250 employees and an annual turnover of not more than €50 million or an annual balance-sheet total of not more than €43 million are eligible for assistance from the SME Office.

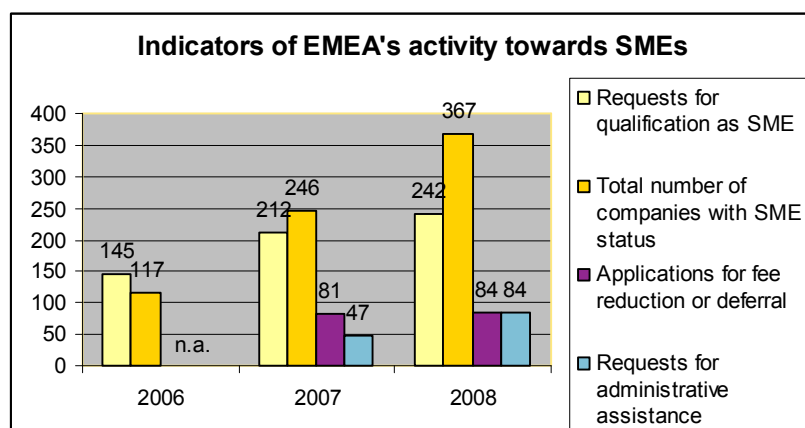


Figure 69: Some indicators of EMEA activity towards SME

Source: EMEA annual reports 2006 to 2008 and complementary sources.

SMEs already benefit from significant fee reductions in most aspects of EMEA-provided services (see Table 7), including, in the case of orphan medicines and advanced-therapy medicinal products, a 50% fee reduction on annual fees in the first year after marketing authorisation. Some SMEs still advocate for a reduction of the annual fee. The deferral and conditional fee exemption benefitting SMEs already allows them to avoid a high expense too early before they get income. However, here again, one should consider whether such an incentive may hinder the ability of EMEA and NCAs to answer the needs with an adequate level of resources.

EMEA Service	Applicable type of product	Reduction
Scientific Advice	All except Orphan medicines (human products) and MUMS (veterinary products)	90% fee reduction to the total applicable fee
	Orphan medicines	100% fee reduction to the total applicable fee
	MUMS (veterinary products)	100% fee reduction to the total applicable fee
Pre-authorisation Inspections	All (human and veterinary)	90% fee reduction and deferral

		products)	
Application for Authorisation	Marketing	All except Orphan medicines and Advance therapy medicinal products	Deferral and conditional fee exemption
		Orphan medicines	100% fee reduction to the total applicable fee
		Advanced therapy medicinal products (subject to proof of a particular public health interest in the Community in the product concerned)	50% fee reduction to the total applicable fee
Scientific Services		All (human and veterinary products)	90% fee reduction
Establishment of Residue Limits for medicinal products	Maximum for veterinary	All veterinary medicinal products	90% fee reduction
Administrative services (excluding parallel distribution)		All (human and veterinary products)	100% fee exemption
Post-authorisation inspections		All (human and veterinary products)	90% fee reduction
Post authorisation activities including annual fees during the first year after marketing authorisation		Orphan medicines	100% fee exemption to the total applicable fee
		Advanced therapy medicinal products	50% fee reduction to the total applicable fee

Table 7: Fee incentives for SMEs under the current European legislation. 60

Source: Explanatory Note on Fees payable to the EMEA, EMEA/199262/2009

⁶⁰ Pursuant to Article 70.2 of Regulation (EC° N) 726/2004, applicants which meet the definition of a micro, small or medium-sized enterprise (SMEs) are eligible for fee incentives from the EMEA. Applicants must be established in the EEA and fulfill the definition of an SME set out in Commission Recommendation 2003/361/EC.

5.4.4. Support to the entry of generic medicines and biosimilars in the market

Facilitating access to generics is considered a key lever both in order to enhance access to medicines and to promote an effectively operating internal market for medicines in Europe.

The introduction of generics in the Centralized Procedure⁶¹, together with proactive policies at the Member States level, have increased the introduction of generic medicines in the EU, both in the veterinary and human sector. In particular, Generic introduction has led to an important increase in the number of centralised applications for human medicinal products and a dramatic increase in referrals workload for veterinary medicinal products. The latter products combine a specific array of issues regarding generics, which we will discuss.

The impact of generic entry is currently debated at various levels. In particular, a reflection paper on the improvement of veterinary pharmaceutical legislation was recently presented by the HMA TFWG HMAv for discussion.⁶²

Human medicines

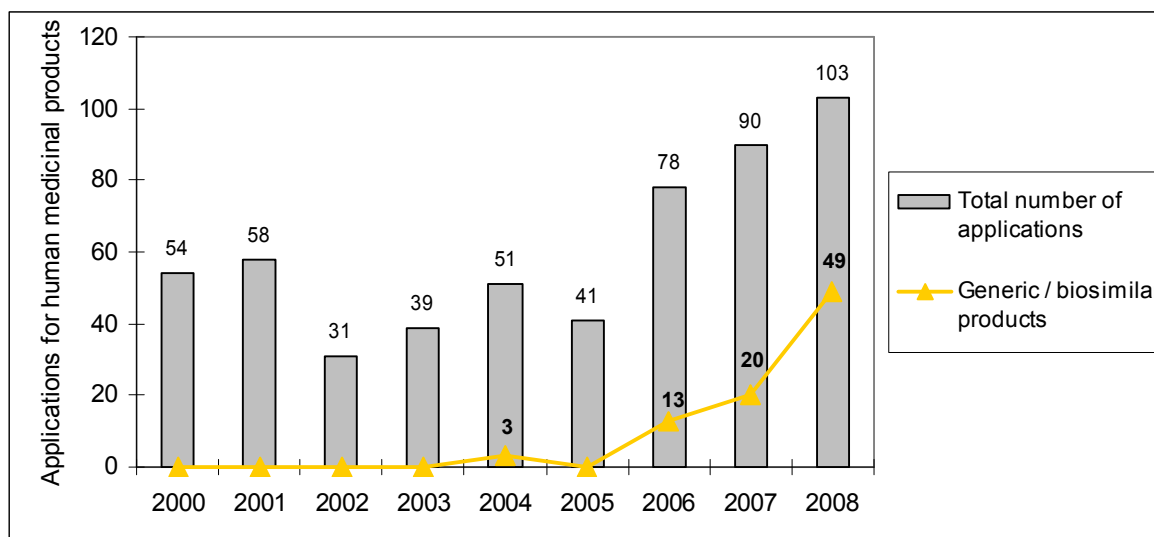


Figure 70: Number of applications for the centralised procedure for human medicinal products by type of application (2000-2008), with a focus on generic / biosimilar applications⁶³

Source: EMEA annual reports (2000, 2001, 2002, 2003, 2004, 2005, 2006, 2007, and 2008)

The access to the centralised procedure has proved very attractive for generic and biosimilar medicines for human use, as can be observed from Figure 70. Since 2005, the number of such applications has grown extremely fast, so as to represent roughly half the applications for centralised procedure in 2008 (49 out of 103), even though the number of positive opinions issued on generics does not precisely

⁶¹ By the application of Article 6 of Regulation (EC) 726/2004 and Article 10 of Directive 2001/83/EC, as amended.

⁶² Published on HMA website on June 2009 : http://www.hma.eu/uploads/media/HMA_TFWG_HMAv_cons_doc.pdf

⁶³ Note that generic applications through centralised procedure are possible since the 2004 regulation (the 3 applications observed in 2004 are biosimilars)

mirror that evolution (see Figure 71). This has had an impact both on the workload of the CHMP and on the workload of working parties, especially when there are issues around bioequivalence.

As generic industry interviewees pointed out, the centralised procedure provides them with a fast, reliable and administratively simplified procedure, and its scientific evaluation level is considered very high. However, many applications for generic still go through DCP, which allows the industry to choose its markets and may for this reason prove less expensive than the CP.

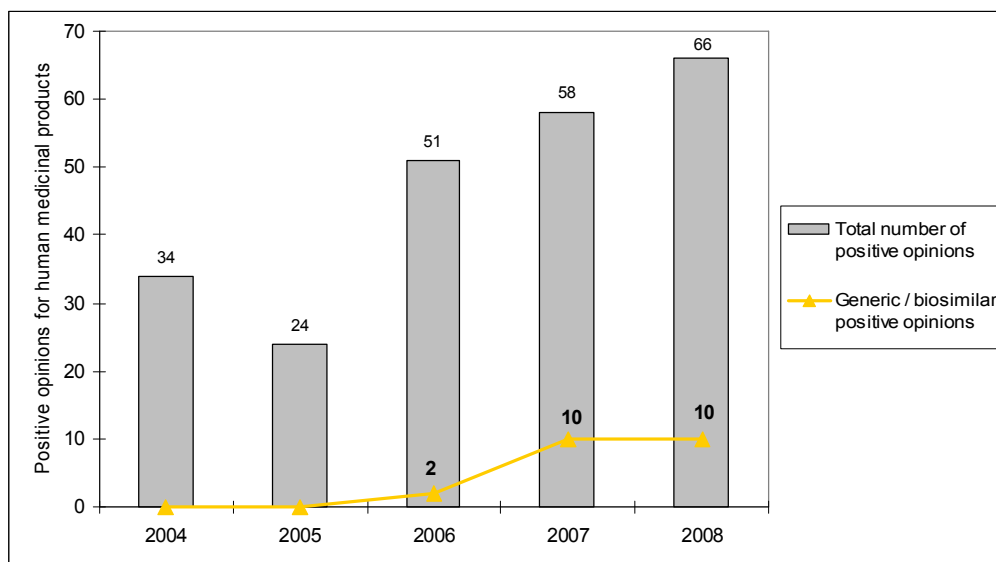


Figure 71: Number of positive opinions for the centralised procedure for human medicinal products by type of applications with a focus on generic / biosimilar positive opinions (2004-2008)

Source: EMEA annual reports (2004, 2005, 2006, 2007, and 2008)

The large increase in the number of applications for generic medicines has led both CHMP members, staff from the Secretariat and NCAs to worry about their ability to match the demand with adequate resources in the coming years.

Veterinary Medicines

The veterinary market differs significantly from the human one, and this has an impact on the adoption of generic medicines.

In particular, veterinary products may not apply to all species, which distribution in turn differs from one country to another in the European Union. In particular, the smaller countries, which are generally the first target for generics because they have a less extended pharmacopeia, may not prove relevant markets because they do not share the same animal species with “traditional” veterinary markets. Thus, the ability to cover all 27 markets at once may not prove as beneficial for the veterinary products as it is for the human ones.

Moreover, the veterinary market is smaller in value than the human one, and each species requests additional specific efficacy and safety data. The costs incurred for marketing authorisation thus represent a higher proportion of development expenses than for the human products, and the Centralised Procedure has often been cited by veterinary industry interviewees as very expensive.

As veterinary product companies tend to select very carefully the markets on which they will launch a product, knowing that the returns will be sensitive to all these factors, the Centralised Procedure also seems less attractive for generics in the veterinary domain than for human ones. Some industry interviewees have confessed that, although the Centralised Procedure did indeed prove more reliable and easier to manage than the DCP, its cost and the inability to choose the markets were an important hindrance for choosing it to launch a veterinary product, including in the case of generic products. Thus,

only big veterinary companies really consider the centralised procedure for products for which it is optional.

This is reflected in Figure 72 and Figure 73, which show the evolution of generic / biosimilar applications and authorisations for veterinary products since 2000. Generic and biosimilar applications for veterinary products still tend to be scarce, and no specific trend is observable. Indeed, as is the case for all veterinary medicinal products, generic veterinary products mainly go through the decentralised and mutual recognition procedures, thus impacting EMEA through referrals mostly (see Figure 74).

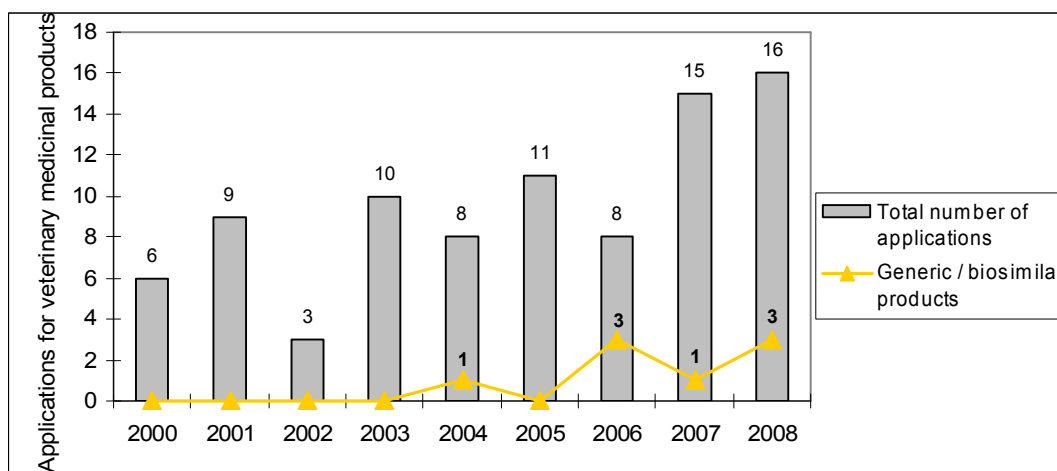


Figure 72: Number of applications for the centralised procedure for veterinary medicinal products by type of application (2000-2008), with a focus on generic / biosimilar applications

Source: EMEA annual reports (2000, 2001, 2002, 2003, 2004, 2005, 2006, 2007, and 2008)

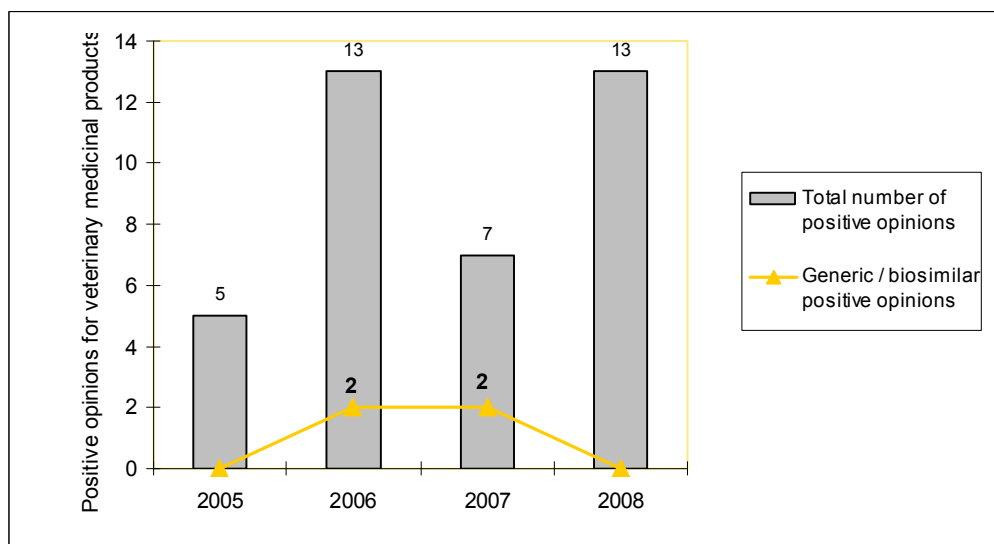


Figure 73: Number of positive opinions for the centralised procedure for veterinary medicinal products by type of applications with a focus on generic / biosimilar positive opinions (2005-2008)

Source: EMEA annual reports (2005, 2006, 2007, and 2008).

As can be seen in Figure 74, generic medicinal products in the veterinary sector still tend to go mainly through DCP and MRP, where they represent a significant and increasing source of workload for NCAs.

DCP, which was introduced in 2005, went from 3 finalised procedures in 2006 to 89 in 2008, while MRP kept pretty stable around 85-95 finalised procedures per year (CMDv/IFAH data, 2008). While part of this increase may be accountable to the EU enlargement, NCAs underline that much is due to the important number of generics application after the enforcement of new laws at the European level to facilitate generics entry. Indeed, CMD(v)/IFAH Survey 2008 reports that out of 89 finalised DCP procedures in 2008, 74 were for generic products (see Figure 74). This significantly burdens NCAs, which in turn impacts the availability of their resources to perform evaluation for the centralised procedure.

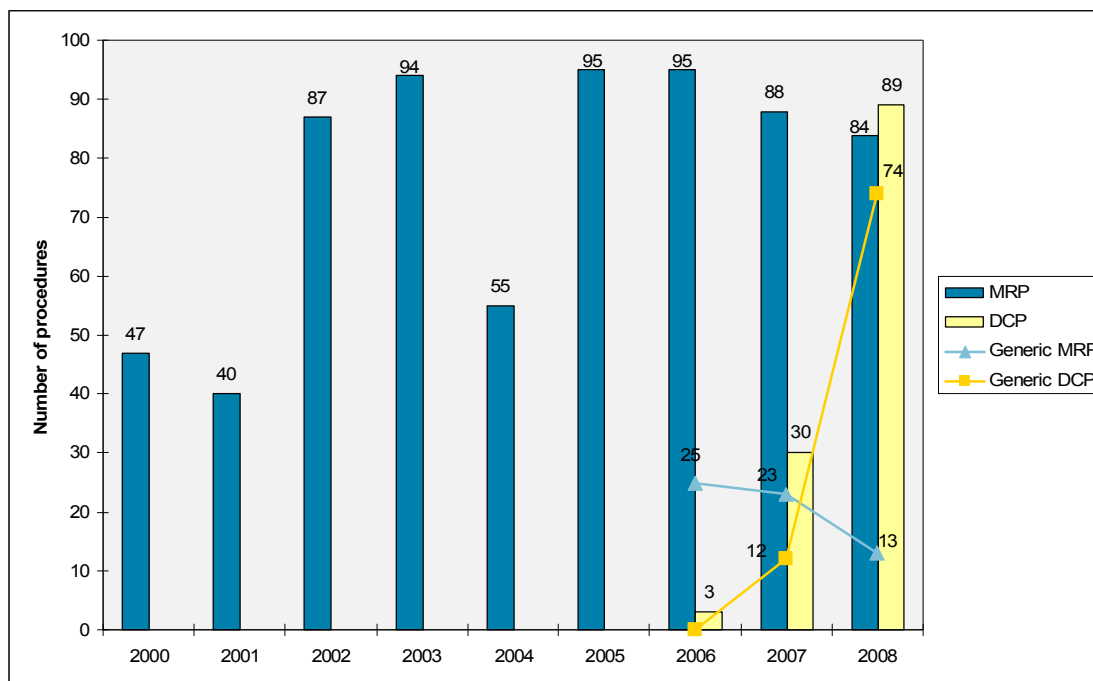


Figure 74: Generics make the most part of the DCP procedures for veterinary medicines. The figure shows the evolution of the number of DCP and MRP procedures for veterinary products from 2000 to 2008, and the part of generics

Source: CMD(v)/IFAH-Europe Survey on the MRP and DCP for veterinary medicinal Products in 2008)

At the EMEA level, although generics only represent about 20% of CP applications, they are often cited as a major source of recent workload increase both by CVMP members and NCAs. This is linked to their high rate of involvement in referrals referred to CVMP. Roughly 10% of MRPs (9 out of 84 in 2008) and DCPs (8 out of 89) are referred to CMDv and half of these make their way to CVMP.

Out of 9 referrals opinions published by the CVMP in 2008, 4 were for generic products, 2 for whole classes of products containing a given API, and only 2 were for specific branded products. In 2007, half of the referrals treated by CVMP were due to generic medicinal products.

The fact that veterinary products apply to different species, in different national breeding contexts leads to a **lack of harmonisation of Reference Products** in the EU. According to CVMP members and NCAs, this is one of the major causes for referrals. In particular, interviewees have often underlined that a given API may be authorized in different countries for various species, with different formulations, and different waiting times.

Indeed, in the case of veterinary medicinal products, the notion of European Reference Product allows applicants to bring forward, through DCP, a generic version of a product that significantly differs from the Reference Product already authorised in a given country (for instance, a generic version of a Hungarian reference product, with a 3 days waiting time may be proposed on the French market, where the matching French reference product is marketed with a waiting time of 5 days). This may lead to confusions on the market itself, where products are presented as similar with two different waiting times.

Moreover, older products may not be able to present data fulfilling the expectations of recent evaluation standards, and some products can even be considered as potentially inefficient. In particular, assessment reports may not be available or may not have been completed to the current standards in force (including products which are supposed to be harmonized, see below).

While the lack of safety data may be supposed to be compensated by the knowledge that the reference product was used for a long time in a given Member State without raising any pharmacovigilance alarm, some assessors still think that these products prove difficult to evaluate and should not be introduced lightly, especially when there is a doubt on their efficacy. First, as we have seen before, pharmacovigilance in the veterinary sector may not be very reliable, in particular because reporting is insufficient. Second, and more importantly, the introduction of products that may show a low level of efficacy or may vary on withdrawal periods and dosages is of particular importance when considering antimicrobials and the risk of emergence of anti-microbial resistance. Indeed, low efficacy products will tend to produce resistance faster, by not getting completely rid of the bacteria targeted. Moreover the variations in usages (timing, length of use) of antibiotics are also a factor known to play a role in the emergence of resistance.

Most veterinary stakeholders agree that anti-microbial resistance is a major issue and should be anticipated as much as possible. Indeed, HMAv has recently agreed over a Strategy of Veterinary Medical Agencies for anti-microbial resistance, launched under the French European presidency and adopted in May 2009. It should be on public consultation soon, aiming at preventing and avoiding anti-microbial resistance that might be the result of inappropriate use of veterinary medicines. EMEA has played an important role in preparing this strategy, and the HMA should publish it by the end of 2009. Although this initiative shows the importance of the subject for major stakeholders, the Commission, EMEA, veterinary and human agencies should probably get more involved and coordinate their efforts in order to end up with a consistent policy towards antibiotics and to avoid any major health crisis both in the human and veterinary domains. This policy will necessarily impact the way generic products are introduced on the market and the harmonisation of reference products across Europe.

Indeed, the variations between European reference products related to the same API are one of the main reasons that lead to an increase in generic referrals. Also, Article 34.2 of Directive 2004/28/EC trusted the Member States to provide the Coordination Group, no later than 30 April 2005, with a list of veterinary medicinal products for which harmonized summary of product characteristics should be prepared. The coordination group then had to agree on a list of medicinal products, on the basis of proposals sent by Member States and forward that list to the Commission. Products on that list were to be subject to the provisions in paragraph 1 of said Directive. This included harmonising their SPCs. However, some Member States may not have completed the harmonisation of SPCs to date. This has sometimes lead to the inability of other states to deliver a Marketing Authorisation to a product used as a generic of the product in the Reference Member State, leading to an article 33 Referral. The fact that the burden of proof in referrals generally rests with the Member State launching a referral and not with the Reference Member State may, in this case, seem inappropriate.

All these reasons have concurred in increasing both the number and the complexity of referrals related to veterinary medicinal products. Indeed, the combination of referral sources and the specific situation of veterinary products with a multiplicity of species, dosages and MRLs lead to complex dossiers. Recently, referrals have been initiated on entire classes of molecules (for instance fluoroquinolones), each of these molecules having often been used in varied ways across the EU for years. These procedures make sense from a public health point of view (keeping in mind the possible co-introduction of similar molecules all over Europe for different usages), but involve the management of hundreds of cases in one procedure, including considerations on dosage, species, ecotoxicity and MRLs for a multiplicity of similar molecules. This kind of referral allows harmonising a whole area of pharmacopeia at once in a consistent way, but also requires important resources. Timelines are hard to manage in this situation, and the CVMP has warned that more of this “super-referrals” are to come if no prior effort is put on harmonising the European Reference Products first. Some stakeholders thus have suggested putting some specific efforts and resources on harmonisation procedures, independently of referrals and with appropriate timelines. On the one hand, this would facilitate the achievement of harmonisation at a national level as expected by Directive 2001/82/EC. On the other hand, it would significantly lighten the CVMP workload, while the CVMP could remain the opinion-issuer at the end of the procedure.

The last issue relating to generic for veterinary medicinal products is eco-toxicity. Stakeholders have brought to the Commission's attention a default in the interpretation of Regulation (EC) No 726/2004. Eco-Toxicity. Some of the recent referrals are due to eco-toxicity assessments for generic veterinary medicinal products and disagreements upon them. Indeed, the way the regulation is written has led to an interpretation requiring a complete eco-toxicity assessment for generic products, although the same assessment is done for the reference product. This situation has two consequences: an increase in referrals over such assessments and an increased protection for reference medicines, since these assessments are very costly. The latter point is of concern as it goes against all the initiatives intended to facilitate generic products entry on the market. Although the wording of the law could easily be corrected, no amendment has been proposed at this time to implement such a change and avoid unnecessary procedures. The Commission has however recently committed to re-evaluate the law.

Sustainability and resources for assessment of Generic medicinal products:

- Many stakeholders have raised the issue of resources to treat generic products-related assessments, both for the veterinary and human products. The steep increase in workload resulting from the 2004 legislation, at the centralised, decentralised and referrals level, may indeed call for a reflection on that matter. Some interviewees, at various levels, point out that a dedicated committee responsible for assessing generics while still leaving the final decision in CHMP (respectively, CVMP) hands would significantly lighten their work. Others have suggested that generics should go through DCP only, but this may only displace the difficulty, since NCAs also report that their resources are already submitted to high generic demand at the DCP and MRP levels.
- Regarding the veterinary products, an important reflection is already ongoing on the harmonisation of European Reference Products. EMEA has a role to play in coordinating these efforts and facilitating access to the appropriate resources to manage the necessary procedures, especially regarding the important issue of antibiotics and resulting anti-microbial resistance.

5.5. Impact on other stakeholders

*To what extent has the EMEA gained trust and provided added value to **other stakeholders**?*

Summary

Although stakeholders acknowledge that scientific assessment performed by the EMEA and decision on the medicine reimbursement is not directly linked, EMEA outputs is recognised as a **key step in a global process leading to pricing and reimbursement**. This process could be further improved by facilitating the communication on valuable information coming from EMEA (e.g. EPAR) useful for pricing and reimbursement step and in particular on arguments on the benefice-risk ratio of a drug.

- ▶ A particular initiative jointly developed by the Swedish medicine agency and then national pricing agency aiming at **building synergies between scientific and costing advice** could be a potent pilot study for EMEA and pricing and reimbursement authorities to consider earlier in the development of a drug the double question of scientific evaluation and costing issue.
- ▶ HTA, pricing and reimbursement bodies acknowledge EMEAs' efforts as well as the constructive collaboration in place and wish to further develop this mutual understanding of the other to reach increased consistency within the whole drug evaluation and marketing process. These bodies are generally highly supportive of such cooperation.
- ▶ Particular areas of improvement for the EMEA in relation to this cooperation with HTA, pricing and reimbursement bodies is the **transfer of useful and needed information** under the appropriate format. EMEA considers this topic as a priority and focuses its effort on the improvement of EPAR to suit to HTA use, the relative effectiveness assessments, as well as the increasing transparency on SPCs issues.
- ▶ A second area of improvement is dealing with **collection and share of relative effectiveness data**. Indeed EMEA's major role in the coordination of pharmacovigilance data collection could be further leveraged by extending this coordination role to relative effectiveness data. This extension of data collection activities should be performed in clear cooperation with HTA bodies.

All stakeholders clearly acknowledge the role of the EMEA as a **recognised actor at international level** as well as a great contributor in the harmonisation of authorisation procedures.

- ▶ Within international organisations (ICH, VICH, WHO, OIE), EMEA has contributed and still contributes to the promotion of international standards through EMEA guidelines.
- ▶ EMEA has developed very strong relationships with its major international partner, the FDA, leading to a long term both formal and information relationship based on mutual trust leading to particular cooperation around common technical working groups, monthly reports, staff exchange, parallel scientific advices, parallel designation of orphan medicines, permanent full-time employee hosting. A remaining area for harmonisation between FDA and EMEA has been suggested to be the clinical trial phases where FDA performs centralised procedures where Europe processes through national agencies.
- ▶ EMEA has already started cooperation with other international medicine agencies such as PMDA in Japan which is clearly highly supportive of such initiatives. Staff exchange remains a greatly appreciated tool to develop cooperation.
- ▶ EMEA has also developed a high quality relationship with other European agencies and in particular around overlapping topics such as infectious diseases and vaccines with the ECDC or

EFSA.

- ▶ EMEA is finally supporting health authorities in developing countries through issuing certificates of medicinal products. Industry stakeholders are welcoming this effort from the EMEA. This support could be further improved in developing the procedure of giving access to an EMEA scientific opinion for developing countries.

All these stakeholders recognise the quality of EMEA contribution at international level, as well as its efforts towards better collaboration.

5.5.1. EMEA is developing greater collaboration with HTA, pricing and reimbursement bodies

Pricing and reimbursement of medicines is dealt with national level by very different bodies interested in EMEA outputs

Pricing and reimbursement authorities are key stakeholders in the marketing process of medicinal product; their action follows the authorisation procedure and it has direct impact on the effective distribution of medicinal products, as well as on patients' access to medicines. As part of the whole process, EMEA has to have some knowledge of the expectations of such bodies, in order to improve the effective access of European citizens and animals to high quality, efficient and safe medicines.

The decision on pricing and reimbursement of a medicines lies with the Member States, which all have very different healthcare systems. Several inputs are considered for such decision, notably evaluations from the EMEA but also from Healthcare Technology Assessment (HTA) bodies, that also are under the responsibility of Member States. HTA, pricing and reimbursement bodies may have very different characteristics depending on the European Member State in terms of:

- ▶ Scope of competencies:
 - HTA, pricing and reimbursement may be for instance under the responsibility of a single entity in some Member States;
 - HTAs are often dealing with medical devices at national level, which is not the case for the EMEA.
- ▶ Link with their respective national competent authorities dealing with marketing authorisations: the relationship with the NCA may be more or less strong. In Portugal for instance, the Human NCA and the agency taking decision on reimbursement are part of the same entity.
- ▶ Decisions on reimbursement: some bodies may have regulatory competencies, when others are responsible for suggesting prescriptions and producing healthcare guidelines for practitioners. In the UK, NICE is in charge of HTA, but also has a significant impact on prescription behaviours through the drafting of guidelines.

All stakeholders agree that scientific assessment performed by the EMEA and decision on the medicine reimbursement should not be directly linked. The EMEA should continue to focus on its core responsibilities as science-based evaluator, looking into the safety, quality, and efficacy of a drug regardless of its economic characteristics. Pricing and reimbursement agencies, at their end, are concerned with economic impacts of medicines, and although they should take into account EMEA and NCA's evaluations of the benefit-risk ratio, they also look into efficiency ratios relative to pre-existing medicines on their market, as well as considering national issues regarding local healthcare systems and costs.

EMEA evaluations and national decisions on pricing and reimbursement are part of the same process and EMEA outputs greatly impact reimbursement decisions, as they provide arguments on the benefit-risk ratio of a drug. In this extent, efforts should be made by all parts to streamline the process where relevant, and facilitate communication on information useful for the next step. Besides, in the context of public finances shortage, the economic part of the benefit-risk analyses is increasingly taken into account. The EMEA should therefore ensure that their documents, especially the EPARs, are clearly pointing out scientific issues at stake, in order to ensure a proper balance.

At Member States level, a lot of NCAs have been given a precise role to inform HTA bodies on effectiveness data. However, there is still a need for more interactions between HTAs and NCAs, given the remaining overlaps and duplications of work, in particular regarding scientific evaluation. One crucial point is the ability of HTAs and pricing and reimbursement bodies to make informed use of EMEA and NCAs' outputs, EPARs included. It seems to be too often the case that the same data is asked twice from the companies in very different formats. This could probably be improved by a better communication between agencies. The following focus points out work in progress in Sweden to improve the collaboration between Swedish human NCA (the Medicinal Product Agencies, or MPA) and the Swedish HTA (DPBA).

Sweden: collaboration with HTA and pricing agency

- ▶ MPA has initiated collaboration with the national pricing agency, the DPBA / TLV (Dental and Pharmaceutical Benefits Agency, DPBA or TLV, is a central government agency whose objective is to determine whether a pharmaceutical product or dental care procedure shall be subsidized by the state).
- ▶ Traditionally, in Sweden, the MPA is in charge of evaluating the safety and efficacy (risk-benefit ratio) of drugs, while the DPBA is in charge of comparing the scientific versus economic benefits of said drug. Here, companies need to satisfy both scientific and cost requirements. That second evaluation (cost-benefit) has reached an unprecedented level of importance recently, with new policies on health costs all around Europe, Sweden included. Big companies generally cope with it pretty well; having resources to anticipate pricing issues, although putting such an emphasis on pricing strategy still is relatively new to companies. Indeed, drugs prices used to be set by companies depending on their efficacy, and were not that much challenged by payers until recently. For smaller companies, this is a very big issue, and they tend not to anticipate the problem enough.
- ▶ MPA annually provides approximately 200 Scientific Advices on medical products. As a pilot, DPBA and MPA have agreed to give joint scientific and costing advice to some companies that solicit them. This pilot program has been running for the past year and will be evaluated at the end of the year. If successful, it will be extended.
- ▶ This program should also end up providing clearer information on what each agency needs in terms of information, on the one hand avoiding duplication of work and loss of time for both the industry and agencies and on the other hand allowing the MPA to better understand the kind of information DPBA is looking for when considering MPA's outputs.

Key learnings:

- ▶ Changing context regarding health expenditures has led the Swedish agency to strengthen its cooperation with the Swedish HTA body. Earlier cooperation between NCA and HTA may allow for
 - a smoother process between the industry, the NCA and HTAs,
 - less duplications of work (clearly defining what kind of information is needed at each level, agreeing on a common format for information that may be needed twice, improving NCA outputs format to better fit HTA specific information needs in scientific evaluation...),
 - and at the end faster and more efficient marketing of medicines in the respect of scientific and cost requirements.

As central European regulatory authority, the EMEA has clearly an important role to play in this increasingly important collaboration. The EMEA Secretariat is already engaged in developing interactions with HTAs, and pricing and reimbursement bodies. Despite differences between Member States' institutional frameworks, common understandings of the information needs could be reached through discussions between the different stakeholders.

Greater collaboration with these bodies are in the interest of all stakeholders

HTA

As mentioned, health-technology assessments differ from EMEA evaluation, but EMEA documents like EPARs are useful contributions. HTA bodies are therefore clearly in favour of further collaborations with the EMEA. Some efforts have already been made on the HTA side, notably through the EUnetHTA project supported by DG SANCO. This initiative was launched in 2005 to support a sustainable and permanent collaboration between HTAs in Europe. It will be reinforced through the setting up of a joint action, formally backed and supported by the Ministries of Health and the Commission, from 2010 onwards. The joint action will be composed of 24 HTA bodies appointed by the Member States plus Norway and Switzerland and will involve all interested stakeholders. It plays also an important role in representing HTAs expectations vis-à-vis external stakeholders like the EMEA. European HTAs wish to keep on building a constructive collaboration based on mutual-respect, in other words in the respect of established allocation of tasks.

Pricing and reimbursement bodies

Payers are also strongly interested in a better cooperation with the EMEA, considering their current use of EMEA outputs. They welcome EMEA efforts in improving its communication towards these bodies.

Industry

Companies often complain about similar information being requested by the EMEA and HTA bodies. The development of interactions between these stakeholders is therefore identified as an important potential improvement. Both are for instance dealing with the same issues related with SPCs. There is an interest of the industry to reach more consistency in the whole process.

The industry is welcoming all recent efforts being made to improve the structure and communication of EMEA benefit-risk assessment towards HTA bodies and to consider how EPAR can further contribute to relative effectiveness assessment.

Besides, the EMEA and HTAs are both using comparative studies in their assessments. There may be different types of comparative studies, more or less focusing on relative effectiveness. However, such studies are very costly for companies. They have therefore great interest not to duplicate the cost of such studies, if they are asked by both stakeholders,

EMEA

At the end, it is also in the interest of the EMEA to develop interactions with these bodies in order to understand properly their expectations and to adapt its communication consequently. The EMEA cannot ignore the following steps of the marketing process leading to concrete distribution of medicines. According to its public health objectives, the EMEA is attaching more and more importance to collaboration with HTAs, especially regarding real life effectiveness.

Concrete fields for improvement have already been identified by the EMEA

Improvement of EMEA documents

It is not an option for the EMEA to deal directly with pricing issues given the above-mentioned allocation of political responsibilities. However, improvement in communication can be reached within the existing framework. The EMEA should continue its efforts to make EMEA outputs understandable and easily usable to all relevant stakeholders.

EMA documents do not always provide HTA, pricing and reimbursement bodies with needed information. Even if EMA objectives are not the same as those bodies' objectives, the Agency collects a lot of information that may be useful for HTA, but this information is not always transmitted in a proper manner. The EMA is already trying to facilitate exchanges with these bodies and is considering this topic as priority. The European Conference on drug effectiveness organised under the Swedish EU Presidency was the occasion to build up this cooperation. Main topics at stake regarding EMA documents include:

- ▶ The improvement of EPARs in order to make them more suitable for HTA use;
- ▶ Greater transparency and cooperation on SPCs issues.

These issues will be also addressed by the Commission/Member States joint action on HTA, as part of an action plan implementing the conclusions of the High Level Pharmaceutical Forum. EMA will be directly involved in these works.

All stakeholders acknowledge that the evolution of EMA collaboration with HTA, pricing and reimbursement bodies is going in the right direction. They expect the EMA to continue improving its contribution through documents showing more consistency and including practical information for all stakeholders. Indeed, one of the main uses of EMA documents is the relative effectiveness assessment done by these bodies.

In line with its post-authorisation activities, the EMA has produced guidelines on efficacy and effectiveness, showing a growing interest on these issues. HTA bodies welcome this evolution but also ask for clarification on the allocation of tasks.

Coordination of data collection related with relative effectiveness

On July 29th 2009, a conference has been held in Stockholm to promote better data collection at the EU level on post-marketing efficacy. This would contribute to adapt pricing policies to effective data observed "in real life" for drugs, especially for very costly ones. Although a lot is done to gather safety data on drugs (Pharmacovigilance), much less is shared on efficacy. Coordination between this Swedish initiative and the deliverables of the joint action on HTA will be ensured.

While pricing and reimbursement policies cannot be harmonised at the EU level at this stage, because systems are way too different and rely on very different situations (not even mentioning some local variations such as observed in UK or Sweden, where drug prices vary depending on the regions where they are marketed), a focus on clinical data per se (focusing particularly on efficacy data), disconnected from pricing and reimbursement issues, could help. Countries could collect clinical data and share it on a European database, each country then being able to translate that data into economic data relative to its own healthcare system (that data may include: days spent at hospital, QALY gained by using such medicine, evaluation of relapse depending on regimen etc...). This would promote both a better use of drugs on the long run, based on better knowledge of its effects and efficacy depending on regimen, and an online adaptation of pricing and reimbursement policies in concerned states. This is also of significant importance if pharmacovigilance watch is to increase in the years to come, as it would provide the right amount of data to get a fair view of the benefit- risk ratio after a medicine is marketed.

As the EMA is already active on the coordination of pharmacovigilance data collection, it could similarly develop the collaboration with HTA organisations regarding the collection of relative effectiveness data. Pharmacovigilance reporting systems could be made to include the collection and share of relative effectiveness data. This is an important area for better collaboration between EMA, NCAs, HTAs and pricing and reimbursement bodies. Some NCAs are already establishing requirements for systematic data collection on day-to-day effectiveness. The EMA, as it already coordinates activities of the NCAs network and developed some tools to do so, could play a major

role in gathering, managing and interpreting effectiveness data.

However, if EMEA moves towards more data collection on effectiveness and relative effectiveness, concept and methodologies should be clarified with HTAs that have experience in this area. More largely, any proposition related with relative effectiveness should be discussed by all relevant stakeholders, i.e HTAs, NCAs, EMEA, patients and industry organisations.

5.5.2. EMEA is contributing actively to the harmonisation of authorisation procedures at the international level

The main objective for the creation of the EMEA was the harmonisation of authorisation procedures at European level, thus contributing to the achievement of an operating internal market. Because of the impact of the regulation in the pharmaceutical market, the further harmonisation of the regulation at the international level contributes to improving the functioning of this globalised market.

EMEA participation to the harmonisation process

In the last few years, there has been a very clear trend towards a global regulatory platform. Thus international work and bilateral connections are very important. The entrance of India, China, Brazil and Russia into the global system definitely has an increasing impact on regulations. As an important actor of the global system, the EMEA should anticipate these changes and accompany them.

NCA's are clearly acknowledging the role of the EMEA as a recognised actor at international level. It is not possible anymore for isolated European NCA's to act as such. They feel they have a stronger voice and more impact on international decisions through the EMEA than if they acted on their own. One preliminary step is obviously to implement European standards, along with promoting international harmonisation and as an example for it.

In terms of international activities, different levels may be distinguished:

- ▶ Within international organisations or projects (ICH, VICH, WHO...);
- ▶ With other regulatory agencies:
 - The FDA as main partner in these harmonisation efforts,
 - Other bilateral cooperations (Japan, Canada, Switzerland, Australia, New-Zealand)
 - With agencies from emerging countries on the issue of good manufacturing and clinical practices (China, India, Brazil...).
- ▶ With external stakeholders at European level (EFSA, ECDC...).

Within international organisations

EMEA is taking part in to international initiatives like the International Conferences on Harmonisation for human (ICH) and veterinary (VICH) medicines. Such projects are aiming at progressively reducing gaps between national regulations. What underpins these projects is that working piece by piece contributes to a more harmonised global environment.

The number of published ICH and VICH guidelines has slightly decreased over time, but EMEA guidelines still contribute as such to the promotion of international standards. Besides, stakeholders seem to have renewed great interest for international harmonisation.

Within this harmonisation process, the industry recognises the EMEA as one of the key regulatory actors.

With the FDA as main international partner

EMEA international activities are mainly based on interactions with the FDA. Throughout the years, both agencies have built a strong relationship. FDA has been involved in the consultation process leading to the creation of the EMEA. Since then, the relationship has grown to both a formal and informal relationship, based on mutual trust.

The main challenge for the EMEA is the fact that the industry tends to follow FDA guidelines, as the major drug health market is the US market. It is therefore important to continue efforts towards harmonisation between FDA and EMEA guidelines to reduce remaining differences.

The industry considers an efficient transatlantic partnership between EMEA and FDA as vital in providing bilateral global leadership in support of innovation.

The current cooperation results from different stages:

- EU-US confidentiality arrangements have been implemented since their signature in September 2003. An important part of the implementation plan published in October 2004 is the parallel scientific advice from the two agencies;
- As a follow up of the Transatlantic Administrative Simplification Workshop, the Action Plan, published in June 2008, identified opportunities for administrative simplification through transatlantic cooperation at the level of administrative practices and guidelines
- A common application format to facilitate parallel submission for orphan designation at the EMEA and the FDA was implemented in 2008;
- Since July 2009, there is one FDA permanent full-time employee at the EMEA and in early 2010 the EMEA Secretariat will send a permanent full-time employee to the FDA.

On a regular basis, EMEA and FDA have exchanges through various means:

- Common technical working groups (« clusters »),
- Formal monthly reports,
- 3-months staff exchanges.

This relationship is particularly important on Pharmacovigilance issues: for instance, sharing adverse-reaction reports is mentioned as being effective in case of crisis, even though the risk-management systems differ between both agencies.

However, the EMEA-FDA collaboration still needs to improve on specific aspects. Industry representatives consider it very important that an efficient parallel scientific advice procedure is put in place. Such collaboration has indeed begun, but is not yet considered as fulfilling expectations. As the assessment methodology is quite different between the EU and the USA, this should not come as a surprise, but one could expect that at least a common package could be agreed upon. At this stage, from the point of view of the industry, the applicant does not really benefit from the parallel scientific advice, as it often ends with two different scientific advices. Companies have therefore more interest to ask both regulatory agencies separately. Efforts are still to be made in this area. Interestingly, cooperation between both agencies seems to be more effective on the paediatric field. A more thorough comparison of the procedure in both cases may underline specific good practices in this regard.

Suggestions have been made on the topic of clinical trials and the difference of process between the USA and Europe. Whereas FDA considers clinical trials from a fully centralised point of view, clinical trials are not currently under the scope of responsibility of the EMEA. They are consequently managed at national levels leading on the one hand to the possibility of small harmonisation discrepancies between European countries and on the other hand to more filing of dossiers with each selected member state for the industry.

Bilateral cooperation with other agencies should be further developed

With other regulatory agencies

Other agencies such as the Japanese one (PMDA) consider that international cooperation should be reinforced and may focus on some areas like safety. According to the PMDA, the best way to improve

cooperation between agencies and to promote international harmonisation is the exchange of persons. The PMDA has also sent one of its staff members to the EMEA, and would appreciate to receive a European representative in Japan. The PMDA is willing to develop international cooperation with the EMEA up to the level of the close cooperation they have established with the FDA.

Confidentiality agreements are also considered as very important steps to formalise the cooperation between agencies.

The EMEA Secretariat is considering international activities as a key current issue: it has created a dedicated job, an international liaison officer, in 2008.

With other European agencies

At European level, EMEA is cooperating with other European agencies, notably with the European Food Safety Authority (EFSA) and the European Centre for Disease Prevention and Control (ECDC). These agencies are sometimes dealing with similar issues, like infectious diseases or vaccines for the ECDC. However, both acknowledge that there is no overlap of responsibilities. Interviewees from these agencies highlight the quality of the interactions with the EMEA. These should be further developed. As pointed out by the EFSA, this could be done through the creation of common databases on chemical substances that may allow a more coherent circulation of information. With the quick development of nutraceuticals and medical food, the strong interest of the pharmaceutical industry for this type of products, and the increasing involvement of scientific questions in this field, further close interactions may be to consider between EFSA and EMEA.

Promotion of good manufacturing and clinical practices

Considering the evolution of manufacturing and clinical practices, inspections issues are gaining importance at international level in two areas:

- ▶ Good manufacturing practices;
- ▶ Clinical trials: data quality and ethical issues.

On the first point, it is in the interest of all regulatory agencies to coordinate inspections in emerging countries, in order to promote harmonisation of inspection standards as well as avoiding any duplication of work. This type of collaboration could take place in the framework of mutual-recognition agreements.

However, at this point, mutual-recognition agreements have neither been very numerous:

- Australia and New-Zealand since 1999 for human and 2001 for veterinary medicines,
- Switzerland since 2002,
- Canada since 2003,
- Japan since 2004,
- Signed in 1998 but not yet implemented with the USA.⁶⁴

Another way to deal with these issues is to build up relationships with agencies from these countries, mainly China and India, in order to increase their awareness of EMEA expectations.

⁶⁴ EMEA annual reports, 2000-2008

5.5.3. EMEA is supporting health authorities in developing countries

According to cooperation objectives (REG 2004/726, article 58), EMEA has to support the work of health authorities outside the European Union, in particular in developing countries. The EMEA contributes to this objective mainly by issuing certificates of medicinal products. EMEA certificates are issued by the EMEA, on behalf of the European Commission, to confirm the marketing authorisation status and also the compliance with good manufacturing practice (GMP) of either products authorised by the European Commission through the centralised procedure or products for which a centralised application has been submitted to EMEA.

The follow-up of this activity (see Figure 75) reveals a great increase of the number of certificate requests received: it has more than doubled and this evolution has been even stronger in the last two years (+28% in 2007 and +38% in 2008).

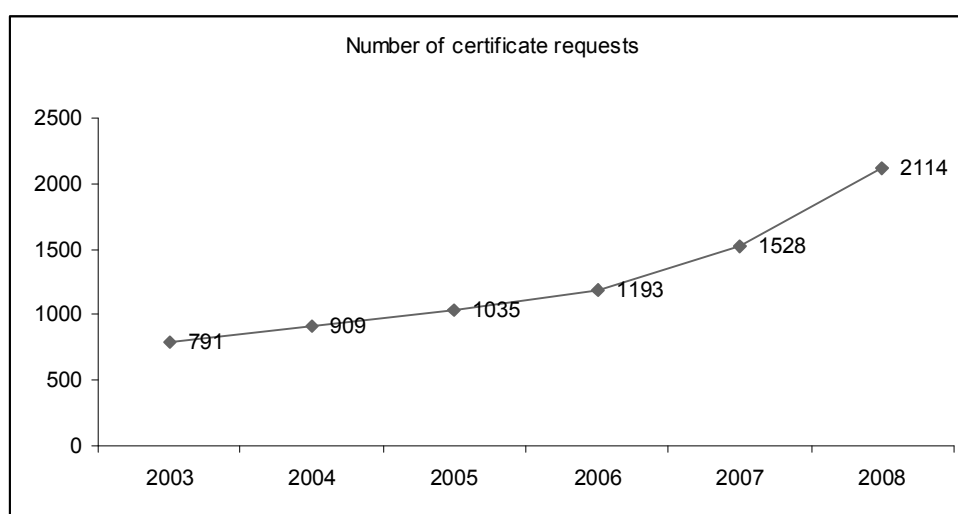


Figure 75: Evolution of the number of certificates requests from 2003 to 2008

Source: EMEA annual reports (2005, 2006, 2007 and 2008)

The industry is recognising and welcoming EMEA efforts to provide assistance and capacity-building in countries with less developed regulatory frameworks. This is more and more relevant in the context of the globalisation of drug development.

Possible room for improvement in this area would be the development of article 58 applications that was not as successful as expected. This article of EMEA founding regulation allows a third country to have access to an EMEA scientific opinion in the context of cooperation of the WHO. The procedural framework exists, but there is still not so much demand. This procedure should therefore more strongly promoted in potentially interested developing countries.

6. Conclusions and recommendations

6.1. Conclusions

Since its creation in 1993, the EMEA has made considerable progress in setting up and maintaining an effective European authorisation system for human and veterinary medicinal products. **In a quite limited timeframe, the EMEA has gained great consideration from all stakeholders**, at European, at Member States level as well as at international level. **EMEA opinions are undoubtedly considered of a very high scientific quality and the Agency has become a leading actor in establishing and contributing to international standards** (human and veterinary ICH guidelines, GCP, GMP ...).

With regards to its mandate, the EMEA has proved **effective in protecting public and animal health** by providing the EU citizens with human and veterinary medicinal products fulfilling the requirements for quality, safety and efficacy. According to legislative changes, the EMEA is supporting the development of medicinal products of major therapeutic interest: all innovative products benefit from the centralised procedure for marketing authorisation, and EMEA implements specific incentives to encourage the marketing of medicines for specific populations (e.g. orphan drugs, paediatric products, MUMS products...). In addition to its **central role for centralised procedures**, EMEA has also **successfully contributed to mutual-recognition and decentralised procedures** through its **involvement in referrals and arbitration procedures**.

The EMEA has clearly contributed to the **harmonisation of EU internal market for medicines**. The centralised procedure offers the opportunity for global access to all European markets through one single entry point. EMEA guidelines and post-authorisation activities are also promoting European standards for the development and use of new medicinal products.

These achievements have been possible thanks to an effective and efficient organisation of the stakeholders involved in the marketing authorisation process. The European Medicines Agency, as a whole including the contribution of 44 National Competent Authorities throughout the 27 EU Member States and the 3 EEA-EFTA countries and the EMEA Secretariat, is the **archetype of an effective community model** with concrete and regular outputs. Despite very heterogeneous NCA models in terms of status, links with their administrations, mandates, and funding systems, despite also various scientific and medicinal traditions, the EMEA is successfully delivering an increasing number of opinions for the authorisation of medicinal products at European level. **A complex system allows the participation of the most relevant European experts** at each stage of the authorisation process.

EMEA Secretariat gives a strong and effective support to this network of experts and especially to the two major opinion-making bodies, the CHMP and CVMP. Its budget has more than tripled between 2000 and 2008, while its scope of responsibilities has been significantly extended and the number of centralised procedures has doubled simultaneously. The EMEA has successfully maintained the same level of quality of the delivered opinions despite this increasing workload and an higher complexity in assessment requirements. **Operational efficiency of this organisation has clearly improved over the last 7 years**.

EMEA as a whole has thus **proved to be a learning organisation that adapts to many different types of changes**: EMEA has adapted successfully to the EU enlargements with new NCAs, to major scientific evolutions such the emergence of advanced therapies and to increasing public expectations in terms of transparency and communication. Cost and process optimisation is also a continuous matter of concern for the EMEA. Working groups and committees are created on a regular and ad hoc basis to deal with emerging issues either on organisational or scientific matters.

Notwithstanding its successes, EMEA faces **difficulties to cope with this increasing workload**. The system has achieved its maximum capacity, especially when considering the workload of the main opinion-making committees (CHMP and CVMP). In addition to some organisational solutions, an increased NCAs involvement is subjected to specific considerations. NCAs do not have a detailed knowledge of the costs incurred by EMEA procedures and the fee coverage of some EMEA activities is

not very clear. Training and capacity building processes for NCAs are also decisive for the proper involvement of the network in the long-term.

The EMEA plays a central role in the marketing of medicinal products, from their development to their distribution and monitoring. The EMEA thus has developed **extensive formal and informal contacts with multiple stakeholders** at local and international levels. The industry is interested in building further such interactions. However, there is still a need for improvement to develop synergies with some specific stakeholders (Health technology assessment bodies, FDA, etc.). The EMEA lacks a clear communication strategy vis-à-vis other stakeholders: patients, healthcare professionals, scientists, HTA bodies, pricing and reimbursement bodies. Each group has specific needs that have to be addressed through dedicated means and processes. NCAs appear to be key intermediaries on these aspects.

EMEA will have to face **novel challenges** in the years to come, including scientific (e.g. the emergence of novel technologies like biomarkers, pharmacogenomics and theranostic), contextual (e.g. aging of population that may in the long-term lead to the need a specific focus on geriatric products) and organizational challenges (e.g. some stakeholders argue in favour of including clinical trials under the scope of EMEA competencies). One may trust the EMEA to adapt to these new challenges as successfully as it has dealt with the previous ones, if its **organisation is appropriately altered in order to ensure the sustainability** of the system.

6.2. Organized and prioritised recommendations

The following paragraphs synthesize the recommendations presented in the whole report. They are organised according to the main themes arising in answers to evaluation questions:

- ▶ Committees organization;
- ▶ Involvement of NCAs in EMEA work;
- ▶ Role of EMEA Secretariat;
- ▶ Procedures;
- ▶ Communication;
- ▶ Industry fees;
- ▶ Telematics;
- ▶ Future challenges.

In each paragraph, recommendations are presented in decreasing priority order. The main improvements for EMEA are captured in the following recommendations: recommendations number 1, 2, 3, 4, 5, 7, 8, 12, 13, 15, 20, 21, 22, 25, 27 and 29.

6.2.1. Committees organisation

Adapting governance and composition rules

- 1. Committees roles and responsibilities, interdependence between committees as well as governance rules between committees and in particular between opinion-making committee and pre-committees have to be more clearly communicated**

Two types of committees should be distinguished within EMEA Committees organisation:

- **“Opinion-making committees”**: committees, such as CHMP, CVMP and COMP, delivering opinions that are directly followed by a European Commission decision. Even though all committees have a scientific advisory function, it is considered that, in practice, the outputs of these “opinion-making” committees are more binding, and have more political impact.
- **“Pre-committees”**: committees, such as HMPC and CAT, preparing the scientific opinion that will be finally made by the CHMP or CVMP. The outputs of these committees are more analogous to working parties but underlining the importance of associated subjects. They intervene in more specific fields of expertise than CHMP, CVMP, and COMP to a lesser extent, and their outcomes inevitably impact the final CHMP/CVMP opinion.

According to this differentiation, resulting roles and responsibilities of each committee should become more obvious and consistent for all types of stakeholders.

- 2. The Member States representativeness prerequisite should be considered mostly in opinion-making committees**

In our view, we can distinguish two models of group composition:

- ▶ **“Member States model”**: the groups are made up with at least one representative per Member State. This model is fully legitimate for opinion-making committees but should also apply for pre-committees when MS representativeness is a key element of the specific field of such committee like the pharmacovigilance subject;
- ▶ **“Expert model”**: independent experts established the groups to gather the required expertise. This model is particularly suitable for Working Parties, Scientific Advisory Groups and Pre-committees on topics with limited available specific resources (CAT, PDCO and HMPC).

MS representativeness prerequisite may sometimes be contradictory with the pursuance for the best expertise and for the most efficient organisation. Indeed, the contribution of some countries may seem irrelevant for some committees, Working Parties or Scientific Advisory Groups. For resources shortage or political reasons, some MS do not have the capacity, or may simply not wish, to give their opinions in all areas.

The group composition has therefore to be considered with regards to the expertise needs and availability in the Member States.

- 3. PDCO should evolve towards a Pre-committee model to reinforce consistency of the whole system**

PDCO is currently a particular opinion-making body focused a very specific field (early paediatric development plan) and producing an opinion not followed by any European Commission decision. The resulting lack of consistency between PDCO, CHMP and Scientific Advice WP had led to consider its role and responsibility more as a pre-committee than as an opinion-making body. PDCO should be considered as a paediatric Scientific Advice preparing the scientific opinion adopted by the CHMP.

4. Some committees could rather evolve towards an expert model to improve the reactivity of the opinion process

The evaluation identified some committees which operate more independently than others. Assessments and evaluations under the responsibility of the CHMP, CVMP and COMP lead to quasi autonomous opinion while the outputs of the other committees –HMPC, CAT and PDCO considering the above recommendation - are more embedded with other actions.

It is therefore recommended that the PDCO, HMPC and CAT organisation evolves towards an “expert model” supervised by the CHMP. This measure will undoubtedly increase the reactivity of the decision process. The guarantee to keep the expertise needed must be taken care of through the establishment of appropriate rules of procedure.

Even though some argue that the independence of a committee support the quality of the opinion, our view is that the benefit of **a two-step process** with the set up of **an expert opinion** by PDCO, HMPC, CAT **balanced by the 30-MS global and more general view** with CHMP or CVMP should increase the objectivity and strengthen the consistency of the final outputs. Moreover, the appointment of experts by the Management Board, or the CHMP, must allow gathering an independent expertise.

Decreasing the workload of opinion-making committees

5. The creation of additional temporary targeted pre-committees for referrals and for generic products could decrease the CHMP and CVMP workload

The additional supervision tasks recommended above will probably overload the CHMP. However, different measures could decrease the current workload of the CHMP. The creation of additional pre-committees for referrals and generics may be solutions to explore. While the assessment work would be the responsibility of these committees, the outcomes of those assessments would be validated by the CHMP (respectively CVMP), in order to ensure the consistency of EMEA opinions.

The composition of those committees must be established according to their goals. While an expert body looks appropriate to express an opinion on generic products, the political impact of the referral decision may require a committee respecting the representativeness of the Member states.

Generally, the areas of expertise concerned by referrals and generics are more accessible than the ones addressed by existing scientific committees. It could therefore be anticipated that the availability of experts would be a relatively less important concern in those cases than for specific pure scientific fields of expertise (advanced therapies for example).

Moreover, there are currently many referrals for generics because very old products have not yet been harmonised across the EU, especially in the veterinary domain. One could assume that the overload due to generics (and the subsequent overload in referrals) may decrease after a period of approximately 10-15 years. The aforementioned referrals pre-committee may thus prove temporary and disappear when the workload of CVMP and CHMP go back to a more manageable level.

6. A regular review of the working groups nebula should lead to a more focused and relevant coordination workload

Various experts bodies such as working parties, scientific advisory groups and even pre-committees (in particular the generic and referral committees mentioned above) should not be considered permanent. Whenever one of these bodies is not considered necessary any more, it should disappear, decreasing accordingly the coordination workload of the CHMP, or CVMP.

6.2.2. Enhancing the availability of experts and NCA involvement

Improving the availability of competent experts for committees and assessment teams

As we have seen, the NCA network generally provides adequate experts both for the committees and the assessment teams. However, NCAs report increasing difficulties to find relevant resources for EMEA work.

For Member States to be able to propose a more varied choice of representatives and assessors, NCAs need to have the adequate resources at their disposition, both in terms of numbers and quality. As we have reported earlier, NCAs worry that the increase in activity may lead in the near-future to a shortage of resources.

On the other hand, external stakeholders observe that Europe can rely on a very large number of potential assessors throughout the EU, although all of them may not be accessible or experienced enough to contribute. While in some countries there may be a lack of expertise because of the recent creation of the medicine evaluation structures, in others the problem is more of having staff that has experience of European procedures (in many NCAs, only a limited number of assessment staff is involved in EMEA activities, other staff being fully devoted to national activities).

Various recommendations may be considered to facilitate NCAs' ability to provide more experts to the European evaluation system when necessary. These are not mutually exclusive options.

The first possibility is to **facilitate the upgrade of NCAs capacities by increasing the number of experts able to engage in European Procedures.**

7. EMEA and NCAs should encourage more experts at the NCA level to be exposed to European procedures, so as to foster harmonisation in evaluation practices and increase the number of knowledgeable experts that could be solicited for any given assessment:

EMEA and Member States share the responsibility in helping NCAs improve their global competence by having more people able to take in charge EMEA evaluations and tasks, both in terms of expertise and experience. Exposure to European procedures can be achieved through training, through staff exchanges between NCAs and through internal turnover of experts assuming European responsibilities within NCAs. While the two latter possibilities are the responsibility of NCAs, the first is and should continue being strongly supported by the EMEA.

The EMEA already provides multiple training programmes to improve NCAs' assessors experience of the European procedures. A significant improvement would be to increase the frequency of such programmes and make them as easily available as possible to NCAs' staff and external experts, by decreasing their cost. According to NCAs' feedbacks, assessor trainings should focus on practical case studies. NCAs especially wish for "on the job" trainings about quality and clinical assessment as complement to EMEA guidelines. EMEA-related IT procedures are another area where trainings are already dispensed but still remain necessary.

An alternative to increasing experts' exposure to European Procedure might be to build a capacity of experts within the EMEA. We do not believe this possibility is appropriate, for the following reasons.

Building an EMEA capacity could be done through a secondment programme, where assessors from NCAs would be seconded for a given period of time to the EMEA. This would entail an important reorganisation of the existing system, giving a new role to both the EC (that would obviously be asked to co-fund such a programme with the NCAs) and the EMEA secretariat (who would take partly or fully in charge the centralised activities, by relying on seconded staff). Although this is a theoretically possible option, a majority of stakeholders argues against it. First, the fact that assessors remain in NCAs is considered at this stage a guarantee that good practices spread at the national level through staff that

contribute to the European procedures. Second, such a secondment system would imply that seconded assessors should be paid by the EC during the secondment period; this would mean a significant increase in the EMEA budget, which does not align with the current need for a limitation of European expenses. Third, this system may prove less flexible than the current one with regards to the expertise of the assessment team: EMEA would have to rely on seconded staff only, while the current system theoretically allows soliciting any relevant expert regardless of his/her belonging to a specific NCA (internal and external experts throughout EU).

An extreme version of this scenario would be to implement an “FDA-like EMEA model”, by having permanent staff at the EMEA performing all evaluations and related activities. At this stage, this option is not considered feasible both because of the aforementioned reasons and because it would not align with the functioning of the EU that relies on Member States involvement.

8. The EMEA should make a better use of the experts in the network by promoting multi-national assessment teams. This should include removing administrative burdens and allowing the EMEA to directly compensate each contributing NCA in proportion to its involvement in the assessment.

As we have mentioned before, the total number of potential assessors throughout the EU is quite significant, due to the ability to rely on 44 NCAs, as well as external experts. However, currently, most assessment teams rely only on the resources of one NCA (the one acting as Rapporteur, respectively Co-Rapporteur), and do not tap into resources beyond its Member State. This is unfortunate for two reasons. First, sharing assessment across NCAs may allow building a more complete, relevant and experienced assessment team, by allowing real access to all the best relevant experts in EU for each assessment. Second, it could also facilitate exchange of good practices between NCAs and enhance exposure of smaller NCAs to European procedures by participating directly to specific parts of the evaluation. Multi-national teams of course have limitations, both in terms of logistics and communication, but they should nonetheless be encouraged by EMEA.

EMEA dossiers are planned sufficiently in advance to find the relevant complementary expertises in the network. Such collaboration could therefore be promoted by the EMEA Secretariat, also for scientific purposes. A suggested way of splitting dossiers, when necessary, would be to discriminate between the Efficacy/Safety sections and the Quality section within predefined limits so as to not make the compensation procedure too complex. However, Rapporteur and Co-Rapporteur should remain responsible of any part they may find relevant to outsource to another NCA depending on its specific expertise.

Multiple examples of multi-national teams have been raised during the interviews for both veterinary and human fields. The most significant difficulty encountered in such cases is the difficulty in redistributing the fees between the various parties involved in the evaluation, especially when the NCA is not the direct recipient of EMEA fees (for instance when fee is transferred to the Ministry in charge of the NCA rather than the NCA itself for national organisational reasons). To overcome this administrative burden for cross payments between NCAs, the EMEA could consider organising the direct payment to each NCA that contributes to the assessment team behind the Rapporteur and Co-rapporteur, relative to a pre-set distribution of activities (for instance efficacy/safety/quality parts of the dossier), with a bonus for the NCA acting as Rapporteur (or Co-Rapporteur), as this agency would take in charge the coordination and review of quality of the evaluation.

9. The EMEA should facilitate NCAs’ ability to identify relevant assessors at the EU level by improving the experts’ database

Even if the lack of resources depends mainly on national recruitment policies, the EMEA Secretariat could facilitate the identification of relevant experts for NCAs facing such problems. Although there is a pre-existing database of experts built by the EMEA, it may not be fully updated, in particular from an independence and transparency point of view, and used to its full potential at this stage. It could prove a valuable tool to facilitate the building of multi-national teams of assessors. This database could be updated on a more regular basis with the help of NCAs.

10. While maintaining strong rules for experts involved in opinion-making committees, selection criteria should be more flexible for experts contributing to assessment teams, in order to facilitate access to experienced assessors

Difficulties are sometimes experienced, when trying to find the appropriate assessor, especially when resources are scarce and / or collaborate with the industry on a semi-regular basis. Specific actions could thus be taken to facilitate access to the best experts in every situation, and to allow them to contribute in relevant ways at all stages of the process. Having access to the maximum of competent experts, while keeping in line with independence rules, will help all countries upgrade their capacity in order to be able to contribute fully to the EMEA in the years to come.

One should discriminate between two different kinds of experts:

- ▶ Experts that participate in the opinion-making committees, in particular CVMP and CHMP: for these experts, independence concerns should come foremost, together with expertise and representativeness;
- ▶ Experts that contribute to the assessment teams. In that specific situation, expertise and experience should be the most important criteria to choose the experts. One could suggest that independence constraints, although crucial, could be made a little more flexible to allow for the best evaluation, keeping in mind that on the one hand this would be balanced by a total transparency on the expert industrial experience and on the other hand all work will be revised at the committee level. This would allow to have access to experts more easily and to provide supplementary resources, including in countries where the structure of institutions make it more probable that experts will have worked with the industry at some point.

Procedures on handling conflicts of interests for experts contributing to assessment teams may be reviewed in a direction allowing the access to a wider spectrum of experts without jeopardising their impartiality. A potential improvement would be to weaken some exclusion criteria regarding the date of the last collaboration with the industry. Currently, experts that worked on the topic for a company 5 years ago might be excluded. This criterion may be looked at in a more pragmatic way, for very specific expertise where NCAs may lack of internal experts and when decision-making is not at stake.

11. The Management Board should be able to choose between multiple candidates when selecting a member of a Committee

Beyond the number of resources, one should consider carefully the availability of the right level and diversity of expertise in each committee. For instance, a lack of experts in Immunology was noticed at the CVMP level.

Currently, experts in each committee are supposed to be chosen on their expertise and experience, taking into account gaps in expertise in the committee. Representatives' names are proposed by their countries. Although the Management Board gives an opinion on the relevance of such propositions with regards to the current composition of the considered Committee, it seems that the Management Board rarely asks a Member State to propose another candidate.

We thus propose to marginally improve the procedure by asking the Member States to propose multiple candidates with various profiles to the Management Board whenever it is possible. This would allow the Management Board to choose the more appropriate candidate to fit all relevant needs for expertise in each committee, while respecting representativeness constraints.

Although it is clear that some Member States may have difficulties in proposing more than one name for each Committee, the range for choice should be extended whenever possible by all Member States that are able to present more than one candidate.

Modus operandi of NCAs involvement

12. The compensation system should be clarified, and a funding system identified for non-fee paid activities

- ▶ Most NCAs report that EMEA compensates the main part of their activity for EMEA, although they express worries over the constant increase of time spent on non-paid activities. Thus, there is a need for a better knowledge of NCAs' costs, as well as the part of their time and resources spent on EMEA-related activities. The on-going Costing exercise should answer some of the questions related to this issue. It is important to underline at this stage that NCAs' involvement should not be considered in charged hours only: for instance, an experienced staff may spend less time on an evaluation than a less-experienced one, but with a significantly better output.
- ▶ Generally, non-fee-paid activities pose an issue, some being partly compensated by the European Union contributions (EC contribution and special contribution for orphan medicinal products), while other are not compensated at all. As paediatric activities in particular have tended to drastically increase recently, it is necessary to reconsider whether such activities should be better compensated for the NCAs, while in the same time carefully assessing the extent of resources needed to face the demand. A common consultation with NCAs regarding the compensation of Orphan and Paediatric activities should be engaged, together with a planning of needed resources and competence in the 5-10 years to come.
- ▶ Eventually, a realistic and identified funding should eventually be associated to each type of assessment activities, whether through fees (that may in certain cases be reconsidered), European funding or national funding. This will only be possible after both the costs at EMEA Secretariat level and at the NCA levels have been tracked. While the EMEA already has a cost tracking system, the current Costing exercise may contribute to better understand the structure of NCA costs related to EMEA activity

The careful consideration of the funding of non-fee paid activities is crucial to ensure the sustainability of the whole system. This clarification will most probably require a strong political engagement of the Member States on this issue.

6.2.3. Ever-adapting the role of EMEA Secretariat to EMEA needs

The EMEA Secretariat work is unanimously recognised as useful and efficient. The recent extension of some of the Secretariat's activities towards more scientific activities (including preparatory work for both the PDCO and COMP) is generally considered positive.

Three areas of improvements may nonetheless be considered

First, as EMEA organisation includes more and more committees, a major role for EMEA Secretariat should be to ensure the consistency of procedures as well as their outputs, especially if these outputs emerge from various committees (ex: PDCO vs. CHMP). EMEA Secretariat should act as a link between all parties of the EMEA system, and not reflect "silos" of activities. The recent change in EMEA Secretariat internal organisation may contribute to that transversal approach, although it is too early to assess its impact.

13. The EMEA Secretariat should strengthen its ability to monitor the consistency of EMEA outputs.

The more EMEA committees and expert groups will differentiate their responsibilities, the more there will be a need for integration and coordination of work activities. We have seen that this coordination and integration are achieved through the human resources organisation and some guidelines for interdependent work activities. The IT network also plays an active role. It helps to manage cross

committees' processes more smoothly. All these levers should be used to reinforce EMEA Secretariat's ability to check for consistency between outputs coming out of various committees or inputs coming out of the same committee on related subjects. EMEA Secretariat could also develop new tools to monitor that consistency is respected and put in place procedures to correct inconsistency when they occur.

14. EMEA Secretariat should put in place specific support for NCAs that need it, focusing on EMEA Secretariat areas of excellence :

- ▶ EMEA Secretariat does not cover all administrative work implied by a Rapporteurship, (e.g. database to follow the authorisation process and the planning of all tasks), which can be an issue for small agencies lacking of resources;
- ▶ EMEA support should focus on particularly appreciated area: legal revision and overview, drafting of proper documentation in good English wording;

Some NCAs wish more support from the Secretariat on communication to industry and patients: the EMEA could be more involved in drafting communication briefings.

15. EMEA Secretariat should alleviate the administrative burden for scientific assessors when the scientific complexity of a dossier justifies it

EMEA formalism is important. When a dossier is scientifically complex, a better balance could be struck between the time spent by experts on scientific matters and the time they spend on formalisation. This could be made possible by putting in place specific administrative support (more resources from the Secretariat) in exceptional cases, to allow the respect of timelines while avoiding compromising the scientific quality of evaluation.

On a broader view, assessments' timetables should be regularly reviewed, with the objective of making the time more valuable for scientific assessment. For instance, the risk for the Product Team Leader is to focus only on deadlines, without putting them into the perspective of scientific issues raised and their consequences in terms of public health.

16. EMEA Secretariat should continue putting specific efforts in quality assurance procedures, to guarantee the appropriate level of quality and consistency of EMEA outputs

As stated in the EMEA Road Map to 2010, the implementation of "a robust quality assurance system [helps] to guarantee the overall quality and efficiency of its operations." The EMEA is already making substantial efforts in this sense, analysing regularly rooms for improvement, and should go further through a greater structuring of this process, putting a specific focus on its ability to ensure consistency between outputs. EMEA currently sets the example in terms of quality of procedures, and should continue to do so.

6.2.4. Improving the procedures

As we have seen, EMEA procedures generally provide a high quality output in satisfying timelines.

Minor improvements may however be suggested for the Centralised Procedure as well as the Guidelines preparation process and the Scientific Advice Procedure.

Centralised Procedure improvements

17. The Centralised procedure could be further streamlined by:

- ▶ **Put the pre-submission meeting earlier in the process and involving systematically the Rapporteur**, to provide as much early constructive feedback as possible to the applicant and improve the quality of applications.
- ▶ **Build a continuity throughout the relationship with EMEA:**
 - Maintain the PTL as single contact point with the EMEA Secretariat, if possible both before and after authorisation
 - Create a single entry point that would coordinate all scientific communication towards the industry and could also be involved in checking the consistency of the messages delivered: currently, there is no formal link between experts nominated as Scientific Advice coordinator and as Rapporteur / Co-Rapporteur for the initial assessment.
- ▶ **Facilitate applicant / EMEA communication while preserving assessors independence:** Although the schedule of members of the committees is already tight, some flexibility in order to arrange complementary discussions with the applicant could sometimes help to provide with a more solid and balanced assessment. This should be taken into consideration, notably for applications with great public health issues.

Guidelines preparation process improvements

18. Implement minor improvements to guidelines preparation process to further strengthen their impact:

- ▶ The transparency of the guidelines preparation process could be made more straightforward by fixing the timelines and making the decision process more explicit (both at the committee level and at the working party level when deciding not to take into account a given comment);
- ▶ Guidelines could be clarified by presenting case studies along with their publications, as well as underlining major changes after an update;
- ▶ Adaptability of assessment could be improved by proposing trainings or annual “up to dates” for guidelines which will not be revised in the upcoming year. This may allow assessors to have up-to-date knowledge regarding science or technologies that may conflict with existing guidelines;
- ▶ More effort could be put in monitoring the way a new guideline may impact others, and communicating on potential effects. This could be assumed by the Secretariat.

Positive initiatives promoting industry’s relevant involvement in guidelines dialogue should continue (focus groups, specific workshops, consideration of comments, and respect of the consultation period)

Scientific Advice procedure improvements

19. Make the Scientific Advice a more streamlined and easily accessed procedure

Scientific Advice is a successful procedure as it stands, but may benefit from:

- ▶ streamlining the pre-submission process;
- ▶ facilitating communication with the industry, maybe by making an entry point more available throughout the procedure (and not providing only written responses);
- ▶ launching a reflexion on fees, especially for Veterinary products.

At this stage, we will not make a recommendation towards an alteration of Scientific Advice to make it binding for the EMEA, although this possibility may be considered. Indeed, currently, the output of the Scientific Advice may come at odds with opinions made both by the PDCO (which provides a kind of binding scientific advice relative to Paediatric Investigation Plans) and CHMP (which at this point may take decisions in direct opposition to scientific advice that was provided earlier in the process). Deviations from Scientific Advice given may be done for justifiable reasons (e.g. due to scientific development that took place between scientific advice and application for authorisation), but the CHMP does not need to justify itself when straying from EMEA scientific advice in the current system.

Again, we should underline that it is of the utmost importance that EMEA put significant efforts in ensuring that no loss of data or major inconsistency without justification should occur between these bodies. This is an important role for EMEA Secretariat (see recommendation 13).

6.2.5. Communication

20. EMEA should pursue its efforts in order to provide clearer, more coherent and targeted messages

As described during the report, the evaluation reveals an inadequate recognition of the EMEA outputs by the EU citizens (patients, healthcare professionals ...).

Two major recommendations resulted from our evaluation:

- ▶ Propose a communication adjusted for each public type concerned, since various outputs inefficiently convey the messages sought after;
- ▶ Strengthen the role of the NCA in the communication strategy, as they are, and must remain, the local relays for EMEA information.

The responsibility for these actions certainly falls to different actors.

Indeed, the EMEA role is mainly to provide technical and scientific assistance to the Commission's decisions in the form of opinions and recommendations. This also means that the Agency's activities need to be fully transparent so that the various players concerned by the Commission's decisions can effectively monitor their operations. It therefore looks appropriate that the EMEA reviews existing means of communication:

- ▶ Improve the EPAR to better suit the HTA uses; increase the awareness of EPARs' information for healthcare professionals,
- ▶ Fine-tune the SPC for the understanding of healthcare professionals,
- ▶ Improve the user friendliness of the website (easier access to SPC, PSUR, ...),

- ▶ Support the use of EudraPharm as communication tool.

Though, EMEA are actually working on actions through various workshops to reach those objectives.

We need to keep in mind that, in addition to the EMEA efforts, **a coordinated action among healthcare agencies and adequate support to the NCA by the Commission** would increase the communication effectiveness

As far as the reinforcement of the NCA role within the communication strategy is concerned, the Commission involvement is necessary.

From an operational point of view, the EMEA is not entitled and do not have the resources to strengthen and manage coordination between Member States. The European Commission should identify measures to support the Member States, and be able to implement them. These measures will probably require that all Member States attain a similar level of resources, which probably means to consider financial incentives to sustain some systems.

Secondly, the Commission must preserve its unity and integrity inherent to its executive function. As such, the Community's institutional system is likely to ensure that the message from the different healthcare agencies (EMEA, EFSA ...) is coherent and consistent one with each other.

6.2.6. Industry fees

There is an on-going project at the Commission level to reconsider EMEA fees level, as well as their transparency.

As this point, two recommendations could nonetheless be suggested.

21. EMEA should facilitate the understanding of its fee structure

The EMEA fee structure includes many different cases, and it may be difficult to navigate for smaller companies. EMEA could provide support to industrials in navigating its fee system by helping them estimate, through a multi-choice web interface, the applicable fee for a given application in a given situation.

22. EMEA should simplify its fee structure

The Commission and EMEA could work jointly on a simplification of EMEA fee structure, while keeping the fairness of fees as an important goal. The Commission is to submit a report to the Council on the implementation of the Fees Regulation (Council Regulation (EC) No 297/95) by 24 November 2010, which may lead to a review of the fees structure. This potential review of fee structure should also consider the sustainability of both EMEA and EMEA stakeholders' involvement, as well as the appropriate level of compensation asked from the industry

6.2.7. Telematics

EMEA IT systems generally provide NCAs and other stakeholders with useful support. However, some minor improvements may be suggested.

23. EMEA Secretariat should continue promoting teleconference tools whenever relevant

EMEA organisation implies numerous travels for representatives to attend committees, working parties, scientific advisory groups and other meetings. Most attendants have underlined the interest of using teleconference systems whenever it is possible and relevant.

EMEA Secretariat should therefore promote the use of a single teleconference system, like Vitero which is preferred by NCAs experts. Technical standards should be also promoted for a proper use of teleconference systems.

24. EMEA and NCAs should reinforce their coordination in all IT-related projects in order to facilitate the emergence of a European IT architecture. EMEA and Member States should also encourage NCA's involvement in the appropriation of EMEA telematics tools

The identified weaknesses of telematics have proved the necessity of an improved coordination between EMEA and NCAs IT strategies. Furthermore, Member States' influence on the IT global architecture is crucial and should be ensured.

EMEA already has put important efforts in providing training and support to help NCAs adjust to EMEA telematics tools, which has led to a general satisfaction of NCAs with the support provided by telematics. However, these efforts should continue to tackle remaining difficulties.

Member States' role in the development and use of the databases must also be improved to ensure consistent transfer of data and a better harmonisation of practices and understanding of the functionalities of all telematics tools available. The HMA should also be involved.

25. EMEA should engage in the evaluation of EudraPharm and EudraVigilance to identify and implement the right improvements

Two major telematics tools made available by EMEA are EudraPharm and EudraVigilance. Both are considered necessary and useful, although there still is room for improvement, both at the EMEA level and at NCAs level, entering data in these databases.

EudraPharm will only be fully functional when the necessary adjustments and harmonisation steps are made at the Member States level. A proper functioning of EudraPharm will directly have a positive impact on EudraVigilance data management system.

6.2.8. Facilitating EMEA adaptation to current and future challenges

As we have been able to report, EMEA has adapted to multiple kinds of challenges throughout its history, and must continue to do so.

One may classify these challenges in five categories:

- ▶ Contextual challenges, like the enlargement of the EU;
- ▶ Current and expected legislative challenges, that may modify the scope of EMEA activities, like the creation of the Paediatric Committee;
- ▶ Scientific challenges, like the emergence of new technologies (e.g. advanced therapies) or modifications of the landscape of healthcare (e.g. theranostics);
- ▶ Public Health challenges, like the emergence of anti-microbial resistance or an epidemics crisis;
- ▶ Societal challenges, like the increasing need for information of all stakeholders, patients included.

Adapting further to the EU enlargement

EMEA has so far well adapted to EU enlargement, with all new members entering the system in the expected timelines and EMEA organisation being re-organised in consequence. At this stage, there still is a need for harmonising the level of competence and involvement of all the NCAs, in alignment with Member States priorities and abilities. An important potential step towards a better organisation would be to define and diffuse NCAs best practices in terms of involvement, resources, competences and practices in the following years.

26. Clarify and share NCA best practices (with all NCAs) related to involvement in EMEA activity and define according monitoring indicators, both on the EMEA and NCA sides

The adaptation to the EU enlargement will probably require a proper framework to assess the performance of each NCA as integrated in the EMEA level (in terms of quality of evaluation mostly), and subsequently facilitate the emergence of objective acknowledgments of the contribution of each agency. This framework should not impact the decision power of the Member States, but can set standard benchmarks against which each NCA could measure its own performance in regards to the EMEA objectives. This tool would be used by NCAs to set objectives related to EMEA activities, as well as identify potential needs for training or exchanges of practices.

The implementation of such best practices could be supported by EC incentives to some Members States to contribute to training of other Member States. These standards should also be set using the output of the BEMA (Benchmark of Medical Agencies) Initiative.

Adapting to recent and future legislative evolutions

Recent legislative evolutions included the Paediatric legislation. As we have seen earlier, the EMEA is currently in a learning phase relative to the Paediatric regulation, even though major efforts have been put in adapting to the novel needs and demands created by this legislation, both at the Secretariat, PDCO and NCAs levels. At the Secretariat and NCAs levels, there is a need for a planning of resources and competences for the following years, as the Paediatric Regulation has made it compulsory for the Industry to submit Paediatric Investigation Plans, and activity is ever increasing. The creation of PDCO has increased the risk of inconsistency between outputs emerging from the EMEA, further underlining the need for a Secretariat acting as a safeguard for consistency throughout EMEA activities (see recommendation relative to Secretariat Role).

27. Transparency of Rapporteurship appointment procedures should be strengthened

The EMEA has defined criteria to appoint Rapporteurship (example: EMEA/124066/2005: Principles, objective criteria and methodology for CHMP rapporteur/co-rapporteur appointment), and to a lesser extent the coordinator of scientific advice. Some efforts are being done to have a more balanced allocation of Rapporteurships between the different Member States (recent procedure for appointment and responsibilities of Rapporteur and Co-rapporteur for procedures regarding veterinary medicinal products).

However, the proposed appointment procedure appears to be not efficiently transparent. There are many obvious measures that could help improving the clarity and encourage. The recommendations to put in practice will depend on the type of appointment considered:

- ▶ assessment of candidates carried out by independent authority on the predetermined criteria;
- ▶ details of conflict of interests of candidate made public;
- ▶ names of appointees and reasons for decisions made public;

- ▶ appointment process to be audited.

While these measures undoubtedly increase the openness and transparency of the process, they may also decrease the efficiency of the process through impact on the cost and timeliness. The disclosure of personal details may also be weighted with privacy concerns of the experts.

EMEA could also involve in more training activities towards NCAs, both to increase harmonisation of working procedures and familiarity with transparency rules.

28. EMEA should keep the lead on harmonising pharmacovigilance procedures and tools at the European level

Many initiatives are currently under way to put more efforts into an efficient, more streamlined and less burdensome pharmacovigilance process. These are among the main objectives of the Commission's proposal to modify the pharmacovigilance legislation which is currently being discussed in the Council and European Parliament. Under this legal proposal, the EMEA will play an important role in coordinating pharmacovigilance activities at Community level and thus need additional resources to assume this extended scope of activities.

EMEA should probably take the lead in improving pharmacovigilance methodologies and analyses, in order to ensure that a novel focus on Pharmacovigilance should not come at odds with the ability to provide European citizens with innovative new medicines with a balanced benefit/risk ratio, both at authorisation time and a few years after.

Constant efforts should be put into streamlining all tools contributing to Pharmacovigilance, including EudraPharm and EudraVigilance. These efforts should be shared both by the EC, EMEA and Member States.

Taking specific measures for the Veterinary Sector

As we have underlined, the Veterinary sector has important specificities, in terms of markets covered (multi-species, major geographical discrepancies, relatively small size of markets as compared to human products), associated regulatory requisites (need for assessing Maximum Residue Limits and Eco-toxicity), and public health challenges (specific case of veterinary Generics, important risk for antimicrobial resistance....). All these specificities argue for a specific treatment of the veterinary case that goes beyond the current split between Veterinary and Human legislations. The Commission is already aware of a proposal made by HMAV on some of these aspects. However, the following recommendations may be made.

29. Take into account specific Veterinary challenges :

- ▶ consider the veterinary side of EMEA as an independent body with highly specific issues that can no longer be solved through mirror solutions of human initiatives
- ▶ launch a reflection on the necessity for amending the veterinary regulation on specific aspects: eco-toxicity assessments, generics;
- ▶ launch a reflection on the appropriateness of market exclusivity or other incentives for MUMS products;

An important reflection is already ongoing on the harmonisation of European Reference Products. EMEA has a role to play in coordinating these efforts and facilitating access to the appropriate resources to manage the necessary procedures, especially regarding the important issue of antibiotics and resulting anti-microbial resistance.

Adapting to recent and future scientific challenges

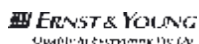
The EMEA should of course anticipate any significant evolution in the health domain and their impact on its activities.

30. Explore potential impact of recent scientific evolutions on EMEA activities:

- ▶ launch a reflection on the middle-to-long-term impact of personalised medicine concepts (e.g. smaller and more well-defined patient population using pharmacogenomics and biomarkers) on future clinical plans, labelling and orphan status designation.
- ▶ launch a reflection on the need for specific competences at the CAT level to face the emergence of theranostics.

7. Appendix

7.1. NCA questionnaire



Evaluation of the European Medicines Agency (EMA)

Your National Competent Authority (NCA)

1 Your NCA (hereafter named "agency")

1.1	Country	
1.2	Name	

1.3 Link between the National authorities and your agency

Your agency is a department of a Ministry	<input type="checkbox"/>
Your agency is subordinated to another institution (ex : Ministry)	<input type="checkbox"/>
Your agency is an independant public body	<input type="checkbox"/>
Other	<input type="checkbox"/>
<i>If Other, please specify</i>	

1.4 Mandate of your agency

Medicinal products evaluation (quality, safety and efficacy)	<input type="checkbox"/>
Delivery of authorisation decisions	<input type="checkbox"/>
Pharmacovigilance	<input type="checkbox"/>
Inspections	<input type="checkbox"/>
Medicinal products pricing	<input type="checkbox"/>
Medicinal products reimbursement decisions	<input type="checkbox"/>
Health technology assessment	<input type="checkbox"/>
Other	<input type="checkbox"/>
<i>If Other, please specify</i>	

2 Person filling the questionnaire

2.1	Name	
2.2	Function	
2.3	Phone number	
2.4	Email address	

3 Does your agency deal with

Human medicines	<input type="checkbox"/>
Veterinary Medicines	<input type="checkbox"/>
Medical devices	<input type="checkbox"/>
Other products	<input type="checkbox"/>
<i>If Other, please specify</i>	

Your perception about EMEA added value

4 Added value of the EMEA

4.1 What benefits does the EMEA provide for your agency?
Please rate the importance (Very important / Important / Less important / Not important) of the following area and possibly describe the added value of each.

In terms of expertise	
Please possibly describe	
In terms of training	
Please possibly describe	
In terms of collaborations with other national agencies	
Please possibly describe	
In terms of sharing the workload related to the authorisation process	
Please possibly describe	
In terms of electronic tools and databases (telematics : EudraVigilance, EudraPharm, EudraGMT, EudraCT...)	
Please possibly describe	
Other (please specify)	
Please possibly describe	

4.2 What benefits does the EMEA provide for your country?
Please rate the importance (Very important / Important / Less important / Not important) of the following area and possibly describe the added value of each.

In terms of public health	
Please possibly describe	
In terms of access to innovative medicinal products	
Please possibly describe	
In terms of the harmonisation of the European market	
Please possibly describe	
In terms of guidelines	
Please possibly describe	
In terms of knowledge to be transferred to national stakeholders	
Please possibly describe	
In terms of the competitiveness of local SMEs	
Please possibly describe	
In terms of information available for patients and healthcare professionals	
Please possibly describe	

6.2a Specific technologies
 Stick if yes, and please specify, as much as possible, how many experts, internal as well as external, in each in 2008. (some experts could cover several area of expertise, but key expertises should be sticked)

Chemical entities (small molecules)	<input type="checkbox"/>	
		experts
Vaccines and Antibodies	<input type="checkbox"/>	
		experts
Gene therapy	<input type="checkbox"/>	
		experts
Cell therapy	<input type="checkbox"/>	
		experts
Other biologics (e.g. : biological peptides)	<input type="checkbox"/>	
		experts
Tissue engineering	<input type="checkbox"/>	
		experts
Other	<input type="checkbox"/>	
<i>If Other, please specify</i>		
		experts

6.3a Specific regulatory aspects expertises
 Stick if yes, and please specify, as much as possible, how many experts, internal as well as external, in each in 2008. (some experts could cover several area of expertise, but key expertises should be sticked)

Safety	<input type="checkbox"/>	
		experts
Efficacy	<input type="checkbox"/>	
		experts
Pharmacovigilance	<input type="checkbox"/>	
		experts
Quality	<input type="checkbox"/>	
		experts
MRL (veterinary)	<input type="checkbox"/>	
		experts
GMP inspections	<input type="checkbox"/>	
		experts
GCP inspections	<input type="checkbox"/>	
		experts
GLP inspections	<input type="checkbox"/>	
		experts
Pharmacovigilance inspections	<input type="checkbox"/>	
		experts
Other	<input type="checkbox"/>	
<i>If Other, please specify</i>		
		experts

6.4a **Specific categories of human medicinal products**
 Specific regulatory aspects expertises
 Tick if yes, and please specify, as much as possible, how many experts, internal as well as external, in each in 2008.
 (some experts could cover several area of expertise, but key expertises should be ticked)

Orphan medicinal products	<input type="checkbox"/>	
		experts
Paediatric medicinal products	<input type="checkbox"/>	
		experts
Herbal medicinal products	<input type="checkbox"/>	
		experts
Advanced therapy medicinal products	<input type="checkbox"/>	
		experts
Other	<input type="checkbox"/>	
<i>If Other, please specify</i>		
		experts

6.5a **Specific activities**
 Specific regulatory aspects expertises
 Tick if yes, and please specify, as much as possible, how many experts, internal as well as external, in each in 2008.
 (some experts could cover several area of expertise, but key expertises should be ticked)

Assessment	<input type="checkbox"/>	
		experts
Scientific advice	<input type="checkbox"/>	
		experts
Guidelines production	<input type="checkbox"/>	
		experts
GMP Inspections	<input type="checkbox"/>	
		experts
GCP Inspections	<input type="checkbox"/>	
		experts
Pharmacovigilance Inspections	<input type="checkbox"/>	
		experts
GLP Inspections	<input type="checkbox"/>	
		experts
Other	<input type="checkbox"/>	
<i>If Other, please specify</i>		
		experts

6.6a	To what extent and in which fields in particular has your agency developed expertise over the five past years?	
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6.7a	Do you consider your agency is particularly strong in any of the subcited fields of expertise? (please specify)	
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If your agency deals with both sectors, Human and Veterinary, please click here to fill in the same questions for Veterinary expertises.

		2006	2007	2008	
7	What is your agency's annual budget in the last three years? (in euros)				euros
	What is your agency's annual budget dedicated in external expertise? (in euros)				euros

		2006	2007	2008	
8	What are your annual income sources in the last three years? (please specify the amount in euros)				
8.1	Government funding				euros
8.2	Dedicated tax				euros
8.3	Locally collected fees				
	for assessments				euros
	for scientific advice				euros
	for inspections				euros
	for other activities				euros
	<i>If Other, please specify</i>				
8.4	Other resources (e.g. : dedicated tax)				euros
	<i>Please specify</i>				

Your agency's involvement in EMEA's activities

9 Workload in 2008 (would be duplicated for Human/Vet in case of agencies dealing with both, could be extended to more years)

If your agency deals with both sectors, Human and Veterinary, please fill in this question 9 first for Human expertises, and at the end click on the specific link to fill in the same question for Veterinary activities.

9.1a How would you evaluate your allocation of resources depending on the various activities
(please specify, as much as possible, how many procedures taken in each in the last three years)
NB: advanced therapy medicinal products are covered in the question

	2006	2007	2008	
National Procedure				procedures
Centralised Procedure (initial applications and variations) as Rapporteur				procedures
Centralised Procedure (initial applications and variations) as Co rapporteur				procedures
Centralised procedure as peer reviewer				procedures
Centralised Procedure as assessor (e.g. member of another agency rapporteur's assessment team)				procedures
Decentralised Procedure as Reference State				procedures
Decentralised Procedure as Concerned State				procedures
Mutual Recognition Procedure as Reference State				procedures
Mutual Recognition Procedure as Concerned State				procedures
Referrals as Rapporteur				procedures
Referrals as Co-rapporteur				procedures
Referrals as assessor (member of another agency rapporteur's assessment team)				procedures
Scientific Advice as coordinator				procedures
Guidelines production as leader				procedures
Paediatric procedure as Rapporteur				procedures
Paediatric procedure as peer-reviewer				procedures
Community herbal monograph or list entry rapporteur				procedures
Community herbal monograph or list entry as peer-reviewer				procedures
GMP inspections				inspections
GCP inspections				inspections
GLP inspections				inspections
Pharmacovigilance inspections				inspections
Pharmacovigilance				assessments
For products under centralised procedure				assessments
For products under non centralised procedures				assessments
Communication towards patients and healthcare professionals				procedures

9.2a Scientific Advice

9.2.1a	Number of requests received by your Agency in 2007	
9.2.2a	Number of requests received by your Agency in 2008	

9.2.3a Specific therapeutic areas
(please specify demands numbers in each)

AIDS	<input type="checkbox"/>		requests
Cancer	<input type="checkbox"/>		requests
Cardiovascular diseases	<input type="checkbox"/>		requests
Central Nervous System	<input type="checkbox"/>		requests
Gastrointestinal	<input type="checkbox"/>		requests
Immunology/vaccines	<input type="checkbox"/>		requests
Infectious diseases	<input type="checkbox"/>		requests
Metabolic diseases and endocrinology	<input type="checkbox"/>		requests
Paediatrics	<input type="checkbox"/>		requests
Other	<input type="checkbox"/>		requests
<i>If Other, please specify</i>			
			requests

9.4a Guidelines production

9.4.1a	To which EMEA guidelines have your staff and external experts contributed in the last three years? (please specify the most significant guidelines)	
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[If your agency deals with both sectors, Human and Veterinary, please click here to fill in the same questions for Veterinary activities.](#)

9.5 Contribution to SAGs and WPs

9.5.1 Scientific Advisory Groups (SAGs)

Which SAGs does your staff or external experts contribute (participate) to?

Scientific Advisory Group on Cardiovascular Issues	<input type="checkbox"/>
Scientific Advisory Group on Anti-infectives	<input type="checkbox"/>
Scientific Advisory Group on Clinical Neuroscience	<input type="checkbox"/>
Scientific Advisory Group on Diabetes/Endocrinology	<input type="checkbox"/>
Scientific Advisory Group on Diagnostics	<input type="checkbox"/>
Scientific Advisory Group on HIV/Viral Diseases	<input type="checkbox"/>
Scientific Advisory Group on Oncology	<input type="checkbox"/>
Scientific Advisory Group on Antimicrobials (SAGAM)	<input type="checkbox"/>

How many staff or external experts from your country contribute to SAGs?		experts
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9.5.2 Working parties (WPs)

Which WPs does your staff and external experts contribute to?

CHMP Working Groups

Biologics Working Party (BWP)	<input type="checkbox"/>
Blood Products Working Party (BPWP)	<input type="checkbox"/>
Cell-based Products Working Party (CPWP)	<input type="checkbox"/>
Efficacy Working Party (EWP)	<input type="checkbox"/>
Gene Therapy Working Party (GTWP)	<input type="checkbox"/>
Joint CHMP/CVMP Quality Working Party (QWP)	<input type="checkbox"/>
Pharmacogenomics Working Party (PgWP)	<input type="checkbox"/>
Pharmacovigilance Working Party (PhWVP)	<input type="checkbox"/>
Safety Working Party (SWP)	<input type="checkbox"/>
Scientific Advice Working Party (SAWP)	<input type="checkbox"/>
Vaccine Working Party (VWP)	<input type="checkbox"/>
Similar Biological (Biosimilar) Medicinal Products Working Party (BMWP)	<input type="checkbox"/>

CVMP Working Groups

Efficacy Working Party (EWP-V)	<input type="checkbox"/>
Immunologicals Working Party (IWP)	<input type="checkbox"/>
Joint CHMP/CVMP Quality Working Party (QWP)	<input type="checkbox"/>
Pharmacovigilance Working Party (PhWVP-V)	<input type="checkbox"/>
Safety Working Party (SWP-V)	<input type="checkbox"/>
Scientific Advice Working Party (SAWP-V)	<input type="checkbox"/>
Environmental Risk Assessment Working Party (ERAWP)	<input type="checkbox"/>

HMPC Working Group

Working Party on Community Monographs and Community List (MLWP)	<input type="checkbox"/>
Organisational Matters Drafting Group	<input type="checkbox"/>
Quality Drafting Group	<input type="checkbox"/>

Other associated Groups

Patients' and Consumers' Working Party (PCWP)	<input type="checkbox"/>
Healthcare Professionals' Working Group (HCPWG)	<input type="checkbox"/>
(Invented) Name Review Group (NRG)	<input type="checkbox"/>
Working Group on Quality Review of Documents (QRD)	<input type="checkbox"/>

Inspectors working groups

GMP inspections	<input type="checkbox"/>
GCP inspections	<input type="checkbox"/>
Pharmacovigilance inspections	<input type="checkbox"/>
GLP inspections	<input type="checkbox"/>

How many staff or external experts from your agency contribute to WPs?		experts
--	--	---------

10 Reasons for contributing

10.1 Why do you accept a rapporteurship (including leadership / co-rapporteurship / peer review / coordination / inspection)?
Please rate the importance (Very important / Important / Less important / Not important) of each criteria.

Because we have the local scientific expertise	
Because we have available resources	
Because it allows to maintain a certain level of expertise (networking, exposure to other experts, exposure to scientific and regulatory evolutions...)	
Because it allows direct participation to the evolution of regulation and guidelines	
Because associated fees represent for the agency significant resources	
Because it facilitates up-to-date knowledge on the evolution of regulation and guidelines	
Because it contributes to our personnel's training	
Because it contributes to our agency's reputation	
Other	
<i>If Other, please specify</i>	

10.2 Are there specific reasons not to accept a rapporteurship? (two choices at the maximum)

Unsustainable additional workload	<input type="checkbox"/>
Unavailable local expertise	<input type="checkbox"/>
Associated financial compensation does not cover incurred efforts	<input type="checkbox"/>
Difficulties in gathering the adequate assessment team (locally or not)	<input type="checkbox"/>
Other	<input type="checkbox"/>
<i>If Other, please specify</i>	

11 Fees and compensations

11.1 Do the fees received from the EMEA compensate for the costs incurred by the initial assessment (pre-authorisation)?
Yes, 100% or more / Yes, mostly (75-99%) / Not quite (50%-74%) / No (>50%)

11.2 Do the fees received from the EMEA compensate for the costs incurred by the post-authorisation activities?
Yes, 100% or more / Yes, mostly (75-99%) / Not quite (50%-74%) / No (>50%)

11.3 In your opinion, should the following activities be compensated? (Yes / No / No opinion)

Referrals (please specify the typology)	
Orphan status assessment	
Services provided to SMEs	
Paediatrics activities	
Herbal activities	
Veterinary activities (where fee reductions are applied)	
Other activities	
<i>If Other, please specify</i>	
Comments	

12 Evolution and sustainability of your involvement

12.1	Has the overall workload related to the EMEA increased (in % of your activity) since 2006? (Yes / No)	
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12.2 In your opinion, what are the reasons for this increase?

Increasing demand from the industry	<input type="checkbox"/>
EU enlargement	<input type="checkbox"/>
Consequences of the recent legislation	<input type="checkbox"/>
Increased patient information expectations	<input type="checkbox"/>
Other	<input type="checkbox"/>
<i>If Other, please specify</i>	

12.3 Possible lack of resources

12.3.1	Does your agency face any lack of resources to dedicate to EMEA-related activities? (Yes / No)	
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12.3.2	Does your agency face any lack of expertises to dedicate to EMEA-related activities? (Yes / No)	
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12.3.3	Does your agency face any lack of resources to dedicate to decentralised and mutual-recognition procedures? (Yes / No)	
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12.3.4 If so, how do you deal with this lack of resources?

By avoiding to take rapporteurship	<input type="checkbox"/>
By limiting your rapporteurship applications to "simple" files	<input type="checkbox"/>
By relying on external expertise (subcontracting)	<input type="checkbox"/>
By limiting your involvement in other EMEA activities (WPs, SAGs, Scientific advice, ...)	<input type="checkbox"/>
Other	<input type="checkbox"/>
<i>If Other, please specify</i>	

12.3.5 Would you reconsider your involvement in EMEA activities?

No, our general involvement is a priority	<input type="checkbox"/>
No, our participation to the committees is a priority	<input type="checkbox"/>
No, our participation is too beneficial for our agency	<input type="checkbox"/>
Yes, the lack of resources is becoming an issue	<input type="checkbox"/>
Other reasons	<input type="checkbox"/>
<i>If Other, please specify</i>	

12.4	Do you consider the current system to be sustainable, considering the high level of reliance on agencies and the increasing workload? (Yes / No / No opinion)	
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12.5	Which factors impact this sustainability?	
	Time spent by assessors (assessment per se, trips, meetings)	<input type="checkbox"/>
	Additional cost for agencies	<input type="checkbox"/>
	Increasing workload due to EMEA activity	<input type="checkbox"/>
	Increasing local workload	<input type="checkbox"/>
	Other	<input type="checkbox"/>
	<i>If Other, please specify</i>	

12.6	Would your agency be able to increase its involvement in the EMEA system in the next few years? (Yes / Only marginally / Not at all / No opinion)	
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In what activities?	
By taking more rapporteurship	<input type="checkbox"/>
By contributing to WPs	<input type="checkbox"/>
By contributing to SAGs	<input type="checkbox"/>
By contributing to peer-reviews	<input type="checkbox"/>
Other	<input type="checkbox"/>
<i>If Other, please specify</i>	

12.7	Please comment on the sustainability of this model	
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Your agency's way of dealing with EMEA activities

13 Please rate the importance (Very important / Important / Less important / Not important) of the following selection criteria when gathering an assessment team (team of assessors/experts assisting the Rapporteur and Co-Rapporteur).

Complementarity of the expert with the rest of the team in a given regulatory domain (safety, efficacy, quality, pharmacovigilance)	
Complementarity of the expert with the rest of the team in a given phase of clinical development (preclinical/clinical)	
Scientific expertise in the therapeutic area of interest	
Expertise in the type of molecule/technology (small/large molecules, advanced therapies...)	
Proximity of the expert to your team (intra-agency, external, other agency)	
Previous interaction with the expert	
Other selection criteria	
<i>If Other, please specify</i>	

14 Do you often contract out any of your assessment work ? (Yes, often (> 50% of files) / Yes, occasionally (10%-50% of files) / Rarely (<10 % of files) / No)

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14.1 If so, in which situation?

On a regular basis, our system relies on such external expertise	<input type="checkbox"/>
Only when we don't have the relevant expertise in-house	<input type="checkbox"/>
When a specific and unexpected problem occurs and needs to be solved rapidly	<input type="checkbox"/>
Other	<input type="checkbox"/>
<i>If Other, please specify</i>	

14.2 What kind of external expertise do you rely on?

Clinical expertise (health professionals)	<input type="checkbox"/>
Regulatory expertise	<input type="checkbox"/>
Scientific/Research expertise (researchers and academics)	<input type="checkbox"/>
Pharmacovigilance expertise	<input type="checkbox"/>
Other	<input type="checkbox"/>
<i>If Other, please specify</i>	

14.3 Which networks do you use?

By relying on your local network	<input type="checkbox"/>
By relying on international networks of your own	<input type="checkbox"/>
By using the EMEA database of experts	<input type="checkbox"/>
Other	<input type="checkbox"/>
<i>If Other, please specify</i>	

14.4 Where do your external experts come from? (please specify the %)

National experts (%)	
International experts (%)	
Please specify if some specific countries are recurrent providers	

15	Does your agency often solicit other agencies to participate to assessment teams? (Yes, often (> 50% of files) / Yes, occasionally (10%-50% of files) / Rarely (<10 % of files) / No)	
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15.1 **How do they do that?**

Through informal discussions at the Committee itself	<input type="checkbox"/>
By using the EMEA database of experts	<input type="checkbox"/>
By relying on pre-existing contacts	<input type="checkbox"/>
Other	<input type="checkbox"/>
<i>Please specify</i>	

15.2 **In such a case, have they experienced difficulties?**

Distance/control difficulties	<input type="checkbox"/>
Language difficulties	<input type="checkbox"/>
Administrative burden (fee distribution, contracts)	<input type="checkbox"/>
Other	<input type="checkbox"/>
<i>If Other, please specify</i>	

16 **Centralised procedure (CP)**

16.1	Do you consider the output of the Centralised procedure to be of good quality? Absolutely (>90% of cases) / Yes (80-89% of cases) / In general (60-80% of cases) / Sometimes (30%-60% of cases) / No (>30% of cases)	
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16.2	Do you consider that the CP should be extended to other products? (Yes / No / No opinion)	
	<i>Please specify which types of medicinal products</i>	

16.3	Do you think the timelines could be shortened? (Yes / No / No opinion)	
	<i>How?</i>	

16.4	Do you think certain aspects of the procedure could be simplified? (Yes / No / No opinion)	
	<i>Please specify which aspects</i>	

17 **Referral procedure**

17.1	Do you consider the output of the referrals to be of good quality? Absolutely (>90% of cases) / Yes (80-89% of cases) / In general (60-80% of cases) / Sometimes (30%-60% of cases) / No (>30% of cases)	
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17.2	Do you think the referral procedures should be compensated? (Yes / No / No opinion)	
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17.3	Do you think the timelines could be shortened? (Yes / No / No opinion)	
	<i>How?</i>	

17.4	Do you think certain aspects of the procedure could be simplified? (Yes / No / No opinion)	
	<i>Please specify</i>	

18 Guidelines	
18.1	Concerning EMEA-produced guidelines, would you say there are (Too many / Not enough / Enough to answer to industry's needs / No opinion)
18.2	Concerning of the topics of EMEA-produced guidelines, would you say they are (Representative of the needs / Inappropriate (too many in some topics, not enough in others) / No opinion)
18.3	Concerning the pace of production of EMEA guidelines, would you say they are (Adapted to the evolution of legislation and technology / Too frequent / Too rare / No opinion)
18.4	Concerning the clarity of the EMEA guidelines, would you say they are (Explicit and easy to understand / Not always clear / Generally unclear / No opinion)

19 Inspections	
19.1	Do you consider the GMP inspections to be of good quality? Absolutely (>90% of cases) / Yes (80-89% of cases) / In general (60-80% of cases) / Sometimes (30%-60% of cases) / No (>30% of cases)
19.2	Do you consider the inspection rate ensures an acceptable level of risk? (Yes / No / No opinion)
19.3	Do you consider the GCP to be of good quality? Absolutely (>90% of cases) / Yes (80-89% of cases) / In general (60-80% of cases) / Sometimes (30%-60% of cases) / No (>30% of cases)
19.4	Do you consider the inspection rate ensures an acceptable level of risk? (Yes / No / No opinion)
19.5	Do you consider the pharmacovigilance inspections to be of good quality? Absolutely (>90% of cases) / Yes (80-89% of cases) / In general (60-80% of cases) / Sometimes (30%-60% of cases) / No (>30% of cases)
19.6	Do you consider the inspection rate ensures an acceptable level of risk? (Yes / No / No opinion)
19.7	Do you consider the GLP inspections to be of good quality? Absolutely (>90% of cases) / Yes (80-89% of cases) / In general (60-80% of cases) / Sometimes (30%-60% of cases) / No (>30% of cases)
19.8	Do you consider the inspection rate ensures an acceptable level of risk? (Yes / No / No opinion)

Your opinion on the current organisation of EMEA

20 Committees

20.1	Do you consider the system of Committees to be effective? (Yes / No / No opinion)	
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20.2 Participation to committees

20.2.1 What are in your opinion, important criteria for selecting a committee's members?
Please rate the importance (Very important / Important / Less important / Not important) of each criteria.

Ensuring an exhaustive level of expertise	
Ensuring representativeness of the Member States	
Other	
If Other, please specify	

20.2.2	Do you consider your agency's level of input at the CHMP to be (Very high / High / Moderate / Low / No opinion)	
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20.2.3	Do you consider your agency's level of input at the CVMP to be (Very high / High / Moderate / Low / No opinion)	
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20.2.4	Do you consider your agency's level of input at the COMP to be (Very high / High / Moderate / Low / No opinion)	
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20.2.5	Do you consider your agency's level of input at the PDCO to be (Very high / High / Moderate / Low / No opinion)	
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20.2.6	Do you consider your agency's level of input at the HMPC to be (Very high / High / Moderate / Low / No opinion)	
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20.2.7	Do you consider your agency's level of input at the CAT to be (Very high / High / Moderate / Low / No opinion)	
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20.2.8	Do you think the COMP, PDCO, CAT, HMPC contribute to decrease the workload of the CHMP? (Yes, strongly / Yes, slightly / Only marginally / No)	
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20.2.9	Do you think the COMP, PDCO, CAT, HMPC contribute to increase the level of expertise in particular areas? (Yes, strongly / Yes, slightly / Only marginally / No)	
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20.3 What are the limits of the current committees' organisation?

Number of members	<input type="checkbox"/>
Increasing workload for a limited number of resources	<input type="checkbox"/>
Limited time of the committee members	<input type="checkbox"/>
Other	<input type="checkbox"/>
If Other, please specify	

21 Secretariat

21.1	How would you evaluate the level of interaction between Secretariat and Committees ? (Very high / High / Moderate / Low / No opinion)	
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21.2 In your opinion, in which fields and to what extent does the EMEA Secretariat provide input ? (please specify the level of input : Very high / High / Moderate / Low / No opinion)

Coordination of assessments and inspections	
Regulatory input	
Secretarial and preparatory work	
Scientific and technical expertise added to the Committees'	
Supervision of the coherence of assessments	
Participation to CMD for referrals	
Entry point for the industry	
Other	
<i>If Other, please specify</i>	

21.3	Do you believe the Secretariat's support should be reinforced? (Yes / No / No opinion)	
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21.4 If so, in which activities

Scientific opinions	<input type="checkbox"/>
Scientific advice	<input type="checkbox"/>
Guidelines production	<input type="checkbox"/>
Other	<input type="checkbox"/>
<i>If Other, please specify</i>	

22 General evaluation

22.1	Do you believe the current centralised evaluation system to provide for the best scientific opinion? Absolutely (>90% of cases) / Yes (80-89% of cases) / In general (60-80% of cases) / Somecases (30%-60% of cases) / No (>30% of cases)	
22.2	Does the current system allow to access the best available experts in your agency? Absolutely (>90% of cases) / Yes (80-89% of cases) / In general (60-80% of cases) / Somecases (30%-60% of cases) / No (>30% of cases)	
22.3	Does the current system allow to access the best available experts in Europe? Absolutely (>90% of cases) / Yes (80-89% of cases) / In general (60-80% of cases) / Somecases (30%-60% of cases) / No (>30% of cases)	
22.4	Do you consider the current system to provide consistent evaluations of similar products across assessment teams? Absolutely (>90% of cases) / Yes (80-89% of cases) / In general (60-80% of cases) / Somecases (30%-60% of cases) / No (>30% of cases)	

23	In your opinion, what are the 3 top issues and challenges with the centralised procedure and with the overall regulatory system in Europe ?	
	1. Issue	
	2. Issue	
	3. Issue	
24	Additional comments: please feel free to provide us with any specific additional comment	

7.2. Interview guides

7.2.1. Interview guide for the industry

A - Interviewee's profile

- **Name:**
- **Company:**
- **Areas of activities:**
- **Function:**
- **Contact:**

B - Objectives of the interview

- Identify the company's expectations towards the EMEA (and other regulatory agencies)
- Evaluate the quality of interactions between companies and various EMEA's bodies and sectors
- Evaluate the level of satisfaction of the company regarding EMEA's activities and services
- Get a better understanding of the respect of procedures for marketing authorisation and identify success factors and bottlenecks

1 - Expectations towards the EMEA

- What are your main expectations towards the EMEA as a whole?
- Do you have specific expectations towards this evaluation exercise?

- What, in your opinion, should EMEA provide pharmaceutical and biotechnology companies with?
 - Scientific opinion
 - Scientific advice
 - Guidance
 - All of the above
 - Other specific support

- How have recent EMEA's evolutions impacted your industry?
 - EU Enlargement and consequences for the EMEA
 - Creation of novel committees : have they a positive added value?
 - HMPC
 - COMP
 - PDCO
 - Recent guidelines evolutions
 - Recent EC proposals
 - Other

2 - Your interactions with EMEA

- How often have you interacted with the EMEA in the past 5 years?
- On what occasion(s) have you interacted with the EMEA?
 - Type of activity
 - Procedure (centralized, referral...)

- PhV (reporting, inspection, other...)
 - Other services (Scientific Opinion, orphan status designation...)
- Product(s):
 - Name
 - Therapeutic area
 - Small/big molecule
 - Branded/Gx
- Which EMEA contact points have you had?
 - Rapporteur
 - Co-rapporteur
 - EMEA Secretariat (which sector):
 - Product Team Leader,
 - Inspection Sector,
 - Other
- For each of your interlocutors, how would you qualify the interaction (in terms of quality/quantity of information received, timing of the procedure, quality of the scientific and/or technical interaction...)?
- How would you compare your company's relationship with EMEA with your company's relationship with other regulatory agencies (local national agency or other regulatory agencies, including non-european)?
- Do you consider that the pharma/biotech industry's opinion has an impact on EMEA?

3 - Services provided by EMEA

- What is your perception of the effectiveness of each of the main processes performed by EMEA? What are their limits?
 - Scientific Opinions:
 - Centralized procedure
 - Referral for mutualised procedure and decentralised procedure
 - Scientific Guidance
 - Pharmacovigilance
 - Inspection services
- Quality of Scientific Opinion
 - Do you believe EMEA's scientific opinions' quality to be
 - Outstanding
 - Very Good
 - Good
 - Average
 - Not-so-good
 - Bad
 - Do you think the EMEA has access to the best possible experts? In terms of
 - Regulatory expertise
 - Therapeutic area-specific expertise
 - Technology-specific expertise (small molecules/big molecules; advanced technologies...)
 - Number of resources and availability

- Has there been on any specific occasion any issue on the choice of rapporteur/co-rapporteur relative to one of your products? If so, how was this dealt with by the EMEA?
- Do you believe the current voluntary involvement of national agencies in the EMEA to be efficient and sustainable? How would you compare it to other, more centralized systems (e.g. FDA)? Does it impact the output on your side?
- Do you consider the current appeal procedures to be sufficient in case of negative opinions issued by the CHMP/CVMP?
- Interest of each procedure for your industry
 - What in your opinion are the respective strengths and weaknesses of the Centralised / Decentralised / Mutual Recognition / National procedures in terms of
 - Quality of the evaluation
 - Cost (absolute and relative to targeted market)
 - Duration and impact on time-to-market
 - Administrative burden
 - Which procedure would you consider the best suited to your activity?
 - Do you believe the centralised procedure should be made compulsory or optional for a wider range of products? If so, for which products?
 - What in your opinion prove to be the bottlenecks of the procedures?
 - Would you recommend modifications of the procedures and why?
 - Scope of the procedures
 - Number of procedures
 - Clarity of the procedure
 - Timelines
 - Teams in charge / experts
 - Other
 - Referral Procedure
 - Have you been involved in a Referral Procedure recently? If so
 - Do you think the current procedure is efficient?
 - Did you understand the final opinion issued by the CHMP (CVMP)?
 - Did you disagree? Why?
 - Do you see specific advantages and drawbacks to the referral procedure?
 - Would you suggest any specific improvement?
- Scientific Advice
 - Have you used the Scientific Advice provided by the EMEA?

If so:

 - Do you think this service provides added value for the industry? Why?
 - What are the main strengths of this service?
 - What are its main bottlenecks?
 - Do you consider the fees to be appropriate?
 - Can you compare this service to the services provided by other agencies?
 - Do you think it should be made compulsory as a pre-authorisation procedure?
 - Do you think scientific advice should be binding for the EMEA?
- Pharmacovigilance
 - Do you find the current PhV procedures effective and efficient?
 - Does the EMEA check the accuracy of the PhV information disclosed by companies?
 - What is your opinion about the evolutions of the PhV expectations in the past few years?
 - Would you expect EMEA to help the industry adjust to the evolutions? How?
 - Do you have any specific opinion on recent EC proposals on Pharmacovigilance?

- Inspections
 - What in your opinion is the role of EMEA relating to Inspections coordination?
 - Do you find the current Inspections procedures appropriate?
 - Do you believe the Inspections results to be of good quality?
 - Have you ever had specific issues regarding the Inspection procedure or inspection teams? How was this taken into account?
 - As Inspections depend on the Member States, do you observe important variations in the way those inspections are conducted across countries?
 - Do you believe the current procedures to be adapted to crisis or emergency situations?
 - In your opinion, are the rate and pace of inspections appropriate? Why?

- Guidelines
 - What is the added value of EMEA's guidelines for your industry?
 - Do you find it easy to understand the current guidelines?
 - Do you find it easy to comply with the guidelines?
 - Do you think the evolution of the guidelines reflect the evolution of the industry and technology or are they too slow/too fast in their evolution? What is the impact of that pace?
 - What impact do guidelines have on your activity? Ex:
 - Facilitate the filing by making the expectations explicit
 - Increase the administrative burden
 - Other
 - Do you see specific improvements needed in terms of guidelines
 - For specific subjects
 - In the way they are made
 - In their wording / clarity
 - Other

- Fees
 - Do you think EMEA's fees are appropriate given the level of expertise and organisation needed to issue scientific opinions?
 - Do these fees compare favourably with those of NCAs or other agencies (FDA, etc.)?
 - Do you think more subsectors should benefit from special arrangements (besides SMEs, orphan drugs, paediatric drugs)
 - Do you think the specific fee arrangements made for SMEs, orphan drugs etc. have had a positive impact?

- Transparency Rules
 - Do the transparency rules followed by the EMEA have any added value for your industry? If so, how?

4 - Perception of Impacts

- What do you think the main strengths and weaknesses of the current authorisation system are?
 - What is your perception of new committees

- Do you think the EMEA currently matches its objectives?
 - In terms of ensuring public health at the EU level
 - In terms of the harmonisation of a European market for medicines
 - In terms of fostering harmonisation of regulation and guidelines at an international level

- Do you think the EMEA contributes to the harmonisation of the market in the EU?

- Do you think the EMEA contributes to the harmonisation of the legislation throughout the EU and the alleviation of the regulatory burden?
- How would you compare the EMEA with (in terms of effectiveness, timing, quality of the opinion issued, quality of the service provided, relative fees)
 - The (national) agency you are most used to work with?
 - The FDA?
 - Other national agencies (Canada, Japan, other)
- Do you think the EMEA-Industry relationships could be improved? In what way?

5 - Specific questions

- For SMEs
 - Do you believe your access to Marketing Authorisation procedures to be facilitated by the current SMEs regulations?
 - Do you think the current SMEs regulations have facilitated innovation in SMEs and thus improved the industry's competitiveness?
 - Do you think more improvements could be made?
- Generics
 - Do you believe the current EMEA's procedures favour the emergence of generics?
 - Have you seen recent evolutions in the way generics are being evaluated?

7.2.2. Interview guide for healthcare professionals' organisations

A. Interviewee's profile

- **Name:**
- **Organisation:**
- **Function:**
- **Address and telephone number:**

B. Objectives of the interview

- Identify healthcare professionals' expectations towards the EMEA (and other regulatory agencies)
- Identify the current forms of interactions between healthcare professionals and the EMEA
- Evaluate the level of satisfaction with this interaction
- Evaluate the level of satisfaction with the information available to healthcare professionals and its use
- Evaluate the perception of EMEA's impact on public health

1- Expectations towards the EMEA

- Would you consider your knowledge of EMEA to be
 - Very basic
 - Limited
 - Good
 - Very good
- What are your main expectations towards the EMEA?
 - In terms of public health
 - In terms of communication towards patients and consumers
 - In terms of communication towards healthcare professionals
 - In terms of Pharmacovigilance coordination
 - In terms of health crisis management (and consequence for healthcare professionals)
 - In other areas
- Are these expectations any different from those you have regarding other regulatory agencies (local NCA, others)?
- How have recent EMEA's evolutions impacted your activities?
 - EU Enlargement and consequences for the EMEA
 - Creation of novel committees
 - Recent guidelines evolutions
 - Recent EC proposals
 - Other
- Do you have specific expectations towards this evaluation exercise?

2- Interaction with the EMEA

- How often have you or your organisation interacted with the EMEA in the past 5 years?
- On what occasion(s) have you or your organisation interacted with the EMEA?
 - Participation to committees, scientific advisory groups or working parties
 - Collaboration on guidelines production
 - Solicitation for specific events (please specify)
 - Reporting of Pharmacovigilance events
 - Other (please specify)
- Which EMEA contact points have you had?
 - EMEA Secretariat (please specify the unit/sector)
 - Committees (please specify the committee(s) and the function of people involved)
 - EudraVigilance actors
 - Indirect contact through a national agency
 - Other (please specify)
- Do you believe the involvement of healthcare professionals has increased recently? Why and how?
- Do you observe discrepancies between healthcare professionals' organisations in terms of their interaction with the EMEA? In your opinion, what are their reasons?

3- Quality of information available to healthcare professionals

- What are, in your opinion, EMEA's objectives?
- Are you aware of the various procedures dealt with by the EMEA and their respective objectives?
- Are you aware of the indications and typology of products for which the centralized procedure is compulsory / optional? Do you see a specific interest for a given indication to be part of this group?
- Have you already accessed any information provided by the EMEA?
 - If so, of what kind?
 - Communication on regulation
 - Communication on specific products
 - Pharmacovigilance information
 - Other (please specify)
 - If so, through which media?
 - Internet
 - Communication through national agencies
 - Other (please specify)
 - If so, how have you used this information?
- Are you satisfied with the information provided on EMEA's website and other media in terms of
 - Content

- Clarity
- Accessibility
- Reactivity to specific events (Pharmacovigilance, crisis management...)
- Use for your practice (please specify)

4- Perception of EMEA's impact

- Do you think the EMEA currently matches its objectives?
 - In terms of ensuring public health at the EU level
 - In terms of the harmonisation of a European market for medicines
 - In terms of fostering harmonisation of regulation and guidelines at an international level
- Are you aware of the following recent evolutions of EMEA? If so, do you believe they have had (or will have) any significant impact for patients? How and to what extent?
 - Creation of the COMP
 - Creation of the PDCO
 - Creation of the CAT
 - Increased focus on Pharmacovigilance and patients information
 - Extension of the indications and type of products for which the centralised procedure is compulsory (including AIDS, cancer, diabetes, neurodegenerative diseases, autoimmune diseases, orphan diseases, products derived from biotechnology) or optional (significant therapeutic, scientific or technical innovation / public health interest)
 - Other
- Do you think healthcare professionals should be more involved in EMEA's activities? How? In which activities?
- To your knowledge, are healthcare professionals more/less involved in other agencies' activities? What is your opinion on these (potential) discrepancies?
- Do you think the EMEA-Healthcare professionals' relationships could be improved? How?

7.2.3. Interview guide for patients and consumer organisations

A - Interviewee's profile

- **Name:**
- **Organisation:**
- **Areas of activities:**
- **Function:**
- **Contact:**

B - Objectives of the interview

- Identify the patients' expectations towards the EMEA (and other regulatory agencies)
- Identify the current forms of interactions between patients organisations and the EMEA
- Evaluate the level of satisfaction with this interaction
- Evaluate the level of satisfaction with the information available to patients and the general public
- Evaluate the perception of EMEA's impact on public health

1 - Expectations towards the EMEA

- Would you consider your knowledge of EMEA to be
 - Very basic
 - Limited
 - Good
 - Very good
- What are your main expectations towards the EMEA?
 - In terms of public health
 - In terms of communication towards patients and consumers
 - In other areas
- Are these expectations any different from those you have regarding other regulatory agencies (local NCA, others)?
- Do you have specific expectations towards this evaluation exercise?

2 - Your interactions with EMEA

- How often has your organisation interacted with the EMEA in the past 5 years?
- On what occasion(s) have you interacted with the EMEA?
 - Participation to committees
 - Collaboration on guidelines production
 - Solicitation for specific events (please specify)
- Which EMEA contact points have you had?
 - EMEA Secretariat (please specify the unit/sector)
 - Committees (please specify the committee(s))
 - EudraVigilance actors

- Indirect contact through a national agency
 - Other (please specify)
- Do you believe the involvement of patients has increased recently? Why and how?
 - Do you observe discrepancies between patients' organisations in terms of their interaction with the EMEA? In your opinion, what are their reasons?
 - Do you believe different patients organisations to have the same expectations towards the EMEA (depending on the indication, the number of patients represented...)? In your opinion, how could EMEA deal with these differences?

3 - Quality of information available to patients

- What are, in your opinion, EMEA's objectives?
- Are you aware of the indications and typology of products for which the centralized procedure is compulsory / optional? Do you think your indication benefits (or would benefit) from being included in the range of products using the centralised procedure?
- Have you already accessed any information provided by the EMEA?
 - If so, of what kind?
 - Communication on regulation
 - Communication on specific products
 - Pharmacovigilance information
 - Other (please specify)
 - If so, through which media?
 - Internet
 - Communication through national agencies
 - Other (please specify)
- Are you satisfied with the information provided on EMEA's website in terms of
 - Content
 - Clarity
 - Accessibility
 - Reactivity to specific events (Pharmacovigilance, crisis management...)

4 - Perception of Impacts

- Do you think the EMEA currently matches its objectives?
 - In terms of ensuring public health at the EU level
 - In terms of the harmonisation of a European market for medicines
 - In terms of fostering harmonisation of regulation and guidelines at an international level
- Are you aware of the following recent evolutions of EMEA? If so, do you believe they have had (or will have) any significant impact for patients? How and to what extent?
 - Creation of the COMP
 - Creation of the PDCO
 - Creation of the CAT
 - Increased focus on Pharmacovigilance and patients information

- Extension of the indications and type of products for which the centralised procedure is compulsory (including AIDS, cancer, diabetes, neurodegenerative diseases, autoimmune diseases, orphan diseases, products derived from biotechnology) or optional (significant therapeutic, scientific or technical innovation / public health interest)
 - Other
-
- Do you think patients should be more involved in EMEA's activities? How? In which activities?
 - To your knowledge, are patients more/less involved in other agencies' activities? What is your opinion on these (potential) discrepancies?
 - In terms of interaction with patients and consumers, how would you compare the EMEA with
 - The (national) agency you are most used to interact with?
 - The FDA?
 - Other national agencies (Canada, Japan, other)?
 - Do you think the EMEA-Patients relationships could be improved? How?

7.3. Bibliography

Type of content	Description of the document
EMEA public document	EMEA annual report 2000
EMEA public document	EMEA annual report 2001
EMEA public document	EMEA annual report 2002
EMEA public document	EMEA annual report 2003
EMEA public document	EMEA annual report 2004
EMEA public document	EMEA annual report 2005
EMEA public document	EMEA annual report 2006
EMEA public document	EMEA annual report 2007
EMEA public document	EMEA annual report 2008
EMEA public document	Budget for 2000
EMEA public document	Budget for 2001
EMEA public document	Budget for 2002
EMEA public document	Budget for 2003
EMEA public document	Budget for 2004
EMEA public document	Budget for 2005
EMEA public document	Budget for 2006
EMEA public document	Budget for 2007
EMEA public document	Budget for 2008
EMEA document	ActiTrak 2003
EMEA document	ActiTrak 2004
EMEA document	ActiTrak 2005
EMEA document	ActiTrak 2006

Type of content	Description of the document
EMEA document	ActiTrak 2007
EMEA document	ActiTrak 2008
EMEA document	Commitment to NCAs by fee type (2006 - 2008)
HMA public document	2008 - Statistics for New Applications (MRP/DCP) and Art.29 CMD(h) Referrals for human medicines
HMA public document	2007 - Statistics for New Applications (MRP/DCP) and Art.29 CMD(h) Referrals for human medicines
HMA public document	2006 - Statistics for New Applications (MRP/DCP) and Art.29 CMD(h) Referrals for human medicines
HMA public document	2005 - Statistics for MRP New Application for human medicines
HMA public document	2004 - Statistics for MRP New Application for human medicines
HMA public document	2003 - Statistics of MRP New Application for human medicines
HMA public document	2002 - Statistics for MRP New Application for human medicines
HMA public document	2001 - Statistics for Mutual Recognition for human medicines
HMA public document	2000 - New Active Substances, Mutual Recognition New Applications Finalised for human medicines
HMA public document	IFAH-Europe / CMD(v) 2007 Survey on the Mutual Recognition and Decentralised Procedure for Veterinary Medicinal Products
HMA public document	IFAH-Europe / CMD(v) 2006 Survey on the Mutual Recognition Procedure for Veterinary Medicinal Products
HMA public document	IFAH-Europe / CMD(v) 2005 Survey on the Mutual Recognition Procedure for Veterinary Medicinal Products
HMA public document	IFAH-Europe / VMRFG 2004 Survey on the Mutual Recognition Procedure for Veterinary Medicinal Products
HMA public document	IFAH-Europe / VMRFG 2003 Survey on the Mutual Recognition Procedure for Veterinary Medicinal Products
HMA public document	IFAH-Europe / VMRFG 2002 Survey on the Mutual Recognition Procedure for Veterinary Medicinal Products
EMEA press release	Report from the CMD(h) meeting held on 19th and 20th January 2009