

# Study on the experience acquired as a result of the procedures for authorisation and monitoring of medicinal products for human use

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Building a better  
working world

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## Glossary

ADR	Adverse Drug Reaction
ASMF	Active Substance Master File
ATMP	Advanced Therapy Medicinal Products
CAT	Committee for Advance Therapies
CESP	Common European Submission Portal
CHMP	Committee for Medicinal Products for Human Use
CMDh	Coordination Group for Mutual Recognition and Decentralised Procedures - Human
CMDv	Coordination Group for Mutual Recognition and Decentralised Procedures - Veterinary
CMS	Concerned Member State
COMP	Committee for Orphan Medicinal Products
CP	Centralised Procedure
CVMP	Committee for Medicinal Products for Veterinary Use
DCP	Decentralised Procedure
EC	European Commission
EEA	European Economic Area
EMA	European Medicines Agency
EMRN	European Medicines Regulatory Network
EPAR	European public assessment report
EU	European Union
FDA	U.S. Food & Drug Administration
GMP	Good Manufacturing Practice
HMA	Heads of Medicines Agencies
HMPC	Committee on Herbal Medicinal Products
ICH	The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
MA	Marketing Authorisation
MAA	Marketing Authorisation Application
MAH	Marketing Authorisation Holder
MNAT	Multinational Assessment Teams
MRA	Mutual Recognition Agreement
MRP	Mutual Recognition Procedure
MS	Member States
NAS	New Active Substance
NCA	National Competent Authority
NCE	New Chemical Entity
OTC	Over-the-counter

PAM	Post-Authorisation Measure
PASS	Post-Authorisation Safety Study
PDCO	Paediatric Committee
PMDA	Japan Pharmaceuticals and Medical Devices Agency
PRAC	Pharmacovigilance Risk Assessment Committee
PSA	Parallel Scientific Advice
PSUR	Periodic Safety Update Report
PSURA	PSUR Single Assessment Procedure
RMP	Risk Management Plan
RMS	Reference Member State
ROG	Regulatory Optimisation Group
RoP	Rules of Procedure
SA	Scientific Advice
SAWP	Scientific Advice Working Party
SME	Small and Medium-sized Enterprise
SmPC	Summary of Product Characteristics
SPOC	Single Point of Contact
TGA	Australian Therapeutic Goods Administration

# Executive Summary

## Objectives and Scope

In line with Article 86 of Regulation (EC) No 726/2004, the Commission shall publish every 10 years a report on the experience required as a result of the operation of the procedures laid down in the European pharmaceutical regulations. In this context, the aim of the study is to assess the extent to which the current marketing authorisation system for medicines meets the objectives laid down in the regulatory framework and ultimately support the evaluation to be published by the Commission. EY was mandated by DG SANTE of the European Commission to undertake this study after a public tendering process.

The study had a number of specific aims:

- ▶ To collect available data and evidence on the operation of the centralised procedure (CP), decentralised procedure (DCP) and mutual recognition procedure (MRP), considering the specific scope of the study;
- ▶ To assess the effectiveness and the efficiency of the procedures and the system in place;
- ▶ To summarise the results of the analysis and draw useful conclusions based on lessons learnt;
- ▶ To compare the current situation with the findings of the 2010 study<sup>1</sup>;
- ▶ To identify options for possible actions which may need to be taken to eliminate any existing barriers and obstacles to optimal performance and analyse the advantages and disadvantages of each option.

The study covered all 28 EU Member States as well as the countries of the European Economic Area (EEA), investigating the time period between 2010 and 2017. As such, it can be seen as a follow-up to the previous evaluation conducted in 2010 under the same legislation. The current study, however, had a more limited scope. It focused on medicines for human use only, with veterinary medicinal products and national products not within its scope. Finally, due to parallel studies being implemented, fees as well as the orphan medicine regulation were not included either.

## Methodology

The study was structured in 5 Work Packages, each including a number of study questions to investigate the effectiveness and efficiency of the system. In line with the Terms of Reference, the Work Packages were structured as follows:

- ▶ **Work Package 1:** The European Medicines Regulatory Network
- ▶ **Work Package 2:** Procedures preceding submission of Marketing Authorisation Applications
- ▶ **Work Package 3:** Initial Marketing Authorisation Procedures
- ▶ **Work Package 4:** Post-marketing authorisation procedures
- ▶ **Work Package 5:** Support activities

To gather the necessary evidence to respond to the study questions under each work package, various data collection tools were used. These included desk research as well as field research. The table below presents an overview of the different tools used.

**Table 1 Summary of Work undertaken to date**

Data Collection Tool	Target Stakeholders	Description
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<sup>1</sup> The report can be found [here](#)

<p><b>Direct Observation</b></p>	<ul style="list-style-type: none"> <li>- EMA Committees</li> </ul>	<p>The Study Team participated in the meetings of 2 Committees: CHMP, and CMDh.</p>
<p><b>Documentary Review</b></p>		<p>The documentary review included the analysis of the relevant EMA annual reports as well as other supporting documentation.</p>
<p><b>Interviews with EMA</b></p>	<ul style="list-style-type: none"> <li>- EMA</li> </ul>	<p>Group interviews were held with the EMA Secretariat in London. Interviews were held for each Work Package with each group interview consisting of 5 individuals.</p>
<p><b>Interviews with stakeholders at EU and international level</b></p>	<ul style="list-style-type: none"> <li>- EC</li> <li>- EU-level umbrella organisations</li> <li>- International organisation</li> <li>- Other agencies</li> </ul>	<p>The Study Team completed interviews with all stakeholder groups foreseen for the study.</p> <p>The following interviews were undertaken:</p> <ul style="list-style-type: none"> <li>▶ European Commission (10)</li> <li>▶ European Parliament (1)</li> <li>▶ Umbrella Organisations (9)</li> </ul>
<p><b>Member States Case Studies</b></p>	<ul style="list-style-type: none"> <li>- 8 Member States</li> </ul>	<p>During the case studies, interviews were conducted with the NCA(s) as well as patient and industry organisations. For these Case Studies, interviews were held with between 3 and 10 people for each Member State.</p>
<p><b>Online Survey</b></p>	<ul style="list-style-type: none"> <li>- Member of EMA committees and Working Parties</li> </ul>	<p>The survey consisted of both closed and open questions and was left open for 3 weeks in March 2019. 288 experts responded.</p>
<p><b>Product Case Studies</b></p>	<ul style="list-style-type: none"> <li>- 20 products</li> </ul>	<p>Product case studies looked at 22 products in detail of which 15 were related to the CP and 8 to the MRP / DCP. Work consisted of a documentary review, with follow-up research undertaken in coordination with the EMA Secretariat and the CMDh.</p>
<p><b>Written Questionnaires</b></p>	<ul style="list-style-type: none"> <li>- NCAs</li> </ul>	<p>The written questionnaires were sent to all NCAs, with 22 NCAs responding. Following the receipt of written responses, interviews were held with Spain and Sweden.</p>

## Legislative Background and Context

**Council Directive 65/65/EEC** first established the fundamental principle that every medicinal product placed on the EU market must have been granted a **marketing authorisation (MA)**. This concept has been further developed and is currently enshrined through two main instruments of the European legal framework, **Regulation (EC) No 726/2004** and **Directive 2001/83/EC**. The two regulatory documents stipulate that for a medicinal product to be placed on the European market, it must hold an MA issued by a **competent authority**. This can either be done via the **Centralised Procedure (CP)**, according to Regulation (EC) No 726/2004; the Decentralised Procedure (DCP) or the **Mutual Recognition Procedure (MRP)**, according to Directive 2001/83/EC; or a purely national procedure.

The two previously mentioned legal documents, together with other complementary legislation, provide the EU regulatory framework. As specified in the terms of reference of the study, the framework for medicinal products has four general objectives:

- ▶ To **guarantee a high level of health protection** for the people of Europe, particularly by providing patients as swiftly as possible with innovative and reliable products and through increased market surveillance thanks to a strengthening of monitoring and pharmacovigilance procedures.
- ▶ To **complete the internal market in pharmaceutical products** whilst taking account of the implications of globalisation and establishing a regulatory and legislative framework that favours the competitiveness of the European pharmaceuticals sector.
- ▶ To **rationalise and simplify the system as far as possible**, thus improving its overall consistency and visibility as well as the transparency of procedures and decision-making.
- ▶ To **meet the challenges of the enlargement of the European Union**.

To investigate to what extent the objectives of the legislation were achieved, the study investigated the functioning of the **European Medicines Regulatory Network (EMRN)**. The network, which is a term not enshrined in legislation but rather put in place to address the needs of the legislation, can be described as a framework in which the various actors work to ensure that patients have access to safe, effective and high-quality medicinal products whilst at the same time providing both patients and healthcare professionals with updated information about medicines. The key actors of the EMRN are **the European Commission, EMA and the National Competent Authorities**.

- ▶ The **European Medicines Agency (EMA)** was founded in 1995 and is a decentralised EU Agency, responsible for the scientific evaluation, supervision and safety monitoring of medicines in the EU.
- ▶ The **National Competent Authorities (NCAs)** are responsible for the marketing authorisations in the respective Member States and provide expertise to the Network.
- ▶ The **European Commission** provides the regulatory basis of the Network, as well as monitoring and overseeing its activities.

These actors work in close collaboration with all the stakeholders involved in the development of medicines, manufacturing, provision and consumption to ensure the objectives of the legislation are achieved. The stakeholder of the EMRN, together with the legislation and organisation in place, is referred to within this study as the **European Medicines Regulatory System**, or the system.

## The European Medicines Regulatory Network

**Over the reference period, the system has increased in complexity** through notably the creation of PRAC and 19 new working parties and new initiatives such as PRIME, which have led to an increased number of days per meeting to cope with the higher workload.

**However, this additional complexity has been endorsed by the system, which has remained overall effective and has adapted to the contextual changes and emerging needs over the past years:**

- ▶ Each actor within the network has a clear and dedicated role, which is recognised by all stakeholders. The committees and working parties provide an adequate space and opportunity to discuss the scientific and regulatory details.
- ▶ The Commission and the Standing Committee fulfil their roles as well.
- ▶ Patient involvement across the network has increased significantly over the study period, which is perceived as a strength of the network.
- ▶ The EMA secretariat is successful in providing effective coordination arrangements and has adapted organisation and working methods in answer to the increased level of activity (+ 10% or above on the majority of tasks), thus contributing to a smooth functioning of the system, as shown by the achievement of performance indicators.

**A need for increased coordination was identified** related to the large number of working parties as well as their temporary nature. Some coordination is lacking on specific tasks endorsed by both EMA and NCA on early advice and the identification of experts.

**The system also has adapted to provide adequate expertise and capacity:** NCA and experts of some MS have increased their involvement, whilst EMA put at disposal both administrative and scientific support as needed. The concentration of rapporteurships on a few, prominent Member States has slightly decreased. Finally, the scientific expertise is adequate to provide strong and credible opinions, even though not provided equally by all MS. Small MS increased their participation through Multinational Assessment Teams (MNAT).

However, in areas that are currently developing and will gain more relevance, **the availability of expertise will need to be ensured in the future.** On a scientific level, this includes most notably ATMPs (Advanced Therapy Medicinal Products) and the intersection of medicines and medical devices. On an operational level, this includes big data and statistical expertise.

**The study period shows an increase in financial and human resources** put at the system's disposal, which is consistent with the development of the system (including the expansion of existing initiatives such as patient involvement and efforts to increase communication and transparency, which also has contributed to a rise in budget):

- ▶ The budget of EMA increased from EUR 208,4 million in 2010 to EUR 331,3 million in 2017 (+60% and an average annual growth of around 6,3%), in line with increase in activities and consequently in fee income (+75% of fees). Expenditures and revenues remained balanced and within the budgetary planning.
- ▶ The number of staff experienced a slight increase from 711 in 2010 to 799 in 2017 (+12%, including contract staff and seconded national experts), to deal with the addition of new activities, both stemming from new legislation, such as PRAC, and self-imposed, such as PRIME.
- ▶ Across the network, most NCAs have increased the resources allocated to EU-level activities over the study period.

On an operational level, whilst the overall length of meetings is accepted by stakeholders, there exists **potential efficiency gains regarding the utilisation of IT, notably through increasing interoperability.**

## Procedures Preceding Submission of Marketing Authorisation Applications

**Pre-submission activities have increased over the study period:**

- Requests for scientific advice have increased from 332 to 471(+42%)
- Support to SMEs has also increased by 50%, with the total number of SMEs registered rising from 1258 to 1893;
- ATMP classifications have increased from 20 to 46 (+130%);
- Orphan designations submitted have increased from 174 to 260 (+49%);
- PIP procedures have increased from 318 to 421 (+32%).



In light of pharmaceutical companies requesting scientific advice more often over the past years, the **resource allocation at a secretariat level seems efficient**. This is furthermore underlined by the fact that EMA has managed to strengthen and implement **procedures to foster competitiveness and accompany the development of innovative products** from an early stage.

- ▶ Mechanisms such as the Innovation Task Force allow stakeholders to experience early opportunities for dialogue, which encourages the development of innovative products.
- ▶ PRIME is a step forward of EMA, to catch up with similar procedures already implemented by e.g. the FDA.
- ▶ The adaptive pathways pilot showed good initiative, but its implementation was not optimal both related to the success rate and the communication efforts. This led to a general scepticism among patient organisations, which can pose a barrier to the effective implementation of a successful pilot.

In general, all types of stakeholders consulted agreed that **the approaches put in place supporting innovation and competitiveness have had a positive impact**. EMA is proactive in trying to develop the support it provides in line with the needs of the market to ensure competitiveness and innovation. At the same time, many NCAs have put in place their own pre-submission assistance mechanisms, such as national innovation offices.

**Scientific guidelines** provide a good documentary basis for pre-submission advice. Nonetheless, their clarity could be improved; and they could be reviewed and updated more frequently, especially regarding innovative areas.

At the EU-level, dedicated **committees and working parties** fulfil their role successfully:

- The SAWP presents an effective mechanism for providing scientific advice;
- CAT provides an opportunity to discuss ATMPs, although its visibility could be increased;
- PDCO plays an important role in paediatric medicines, but its role with respect to the CHMP needs to be strengthened and the PIP procedure simplified;
- Orphan designations by COMP could be better aligned with CHMP decisions.

There are some potential **efficiency gains** regarding cooperation and coordination. Notably, these concern committee coordination, repartition of early stage advice between EMA and NCAs, as well as the cooperation between HTA bodies and EMA/NCAs, to ensure products that go through the EMA procedures will eventually reach the market. **Legislative exceptions** such as compassionate use allow the system to show flexibility in specific cases.

**International cooperation** increased harmonisation through joint GMP inspections and bilateral agreements. Thus, through both European and international efforts, there exists a solid basis to ensure both the quality of scientific outputs and the safety of patients.

Whilst the system is functioning well, it is important to ensure that its achievements are not tainted by a perception of bias, which could arise through cooperating too closely with the pharmaceutical industry on pre-submission advice. The inquiry of the Ombudsman confirms that **clear and formalised procedures are necessary to ensure the trust in the system persists**.

## Initial Marketing Authorisation Procedures

The Centralised Procedure (CP), Mutual Recognition Procedure (MRP) and Decentralised Procedure (DCP) **play a pivotal role in ensuring a high level of health protection for EU citizens** by providing swift access to reliable and innovative medicinal products whilst **supporting the competitiveness of the European Pharmaceutical sector**.

**The co-existence of different procedures is a strength of the EU current system**, which supports the competitiveness of the Pharmaceutical industry within the EU:

- ▶ The different procedures are **well-adapted to deal with existing types of medicines**: the list of medicines for which the centralised procedure is compulsory is adequate, with a majority of new, innovative medicines passing through the centralised authorisation procedure in order to be marketed in the EU.

- ▶ The **ability to choose** between CP, DCP, MRP or purely national procedures is fully adapted to other types of medicines such as generics, for which the three main procedures provide a wide array of options for applicants. The CP provides a solid and robust procedure, which is preferred by research-based companies; whereas MRP and DCP allow country selection, where the choice for commercial and reimbursement decisions are generally considered.
- ▶ **The system is flexible and attractive** for companies that know the advantages and disadvantages of the different types of MA and related procedures from both theoretical and practical points of views.

**Initial marketing authorisation procedures overall comply with legally binding maximum regulatory deadlines.**

- ▶ **The CP regulatory timeframe is appropriate** and would be difficult to reduce further, given the specific environment in which it operates. Compared with other international regulators, the median approval time for new active substances by EMA is slower but remains adequate overall, with various mechanisms that allow quicker access to the market for some medicines. The industry has been calling for even shorter deadlines and a wider use of accelerated procedures. But this does not clearly reduce EU competitiveness and most New Active Substances authorised globally are brought to the European Market quickly, although differences between Member States can exist.
- ▶ **Increased visibility of DCP and MRP timeframes** would be welcomed given the high level of heterogeneity across MS.

**Initial marketing authorisation procedures provide for transparent and clear steps, but they require a high level of workload for experts and heavy procedural infrastructure with EMA and the network.**

- ▶ As the CP involves duplicate procedures and formal involvement of NCAs from all MS, it **requires a lot of capacity**, which the system has been able to deal with so far. However, in the light of rising workloads, there is a need to focus on what is critical and complex, so as to not overburden the system. More specifically, a differentiated approach could be envisaged depending on the products, allowing CHMP to focus on first-in-class medicines, ATMPs and NCEs. Increased flexibility, more informal collaboration and simplified decision-making could be adapted for generics, which currently follow the same timelines as innovative medicines and represent a high workload for the CHMP. CP administrative burden could also be reduced by further exploiting the added-value of peer review (as all MS can comment anyway) and simplifying the assessment report templates.
- ▶ Regarding the DCP and MRP, **procedures are less burdensome for the system, though less transparent, predictable and efficient** for applicants themselves due to inconsistencies and an unharmonised application of the regulation across Member States. The current MRP process allows countries to have additional requirements and administrative controls, which leads to procedures being delayed in frequent cases.

**The three procedures include robust and consistent measures to ensure that suitable and reliable products are marketed and guarantee a high level of health protection for EU citizens.** This also relies on the high level of scientific expertise involved within the network as well as the quality of delivered opinions (based on opinions and factual evidence), with benefit/risk assessment decisions that are also transparent to the public. The rapporteurship is allocated to the relevant experts, although it could be rendered more transparent.

## Post-Marketing Authorisation Procedures

Pharmacovigilance activities, referrals and variations provide a **solid framework for post-marketing authorisation activities** to achieve the objective of strong market surveillance and monitoring:

- ▶ **ADR reporting** mechanisms have been expanded continuously, especially regarding patient involvement, with patient submitted ADRs rising from 19,184 in 2011 to 90,385 in 2017.
- ▶ **The review procedure of ADRs** allows the identification of potential risks and give EMA and NCAs the possibility to take necessary regulatory steps. Around 2,000 signals are detected each year, leading to around 100 validated signals each year.

The identification of risks could be further improved by integrating real world data into the procedures, an undertaking that would require building expertise on big data and statistics.

**The administrative burden** on Variations and Risk Management Plans can be reduced.

- ▶ **Variations**, although effective, come with significant administrative burden, as each variation requires a validation by an NCA. The high number of Type IA variations (around 3,000 per year) mean a simplified system would present significant efficiency gains.
- ▶ Full **Risk Management Plans** for generics do not seem to be necessary, as the active substances have been known for a long time and the full safety profiles are detailed in the pharmacopeia, making all relevant information readily available.

The new pharmacovigilance legislation has **increased the robustness of post-authorisation activities** in general. Notably, the creation of PRAC in 2012 has provided a more formalised setting for pharmacovigilance activities in taking on a coordinating role among the various tools such as Risk Management Plans (RMP), the Periodic Safety Update Reports (PSUR) and the Post-Authorisation Safety Studies (PASS). This puts into question the relevance of **renewals**. With strong monitoring activities in place, a formalised review of the authorisation after 5 years no longer seems necessary.

The greater coordination efforts have also led to a constant decrease in **referrals**, with the diminishing frequency outweighing the complexity of the procedure.

Beyond the monitoring of authorised medicines, **EU coordination mechanisms to respond to health threats are working well**, as evidenced by the H1N1 outbreak. However, the area of medicine shortages remains a risk, as EU coordination mechanisms are not yet formalised and data availability is generally low.

## Support Activities

**EMA Telematics provide significant added value**, and tools such as the Eudragilance database are a strength of the system. EMA recognised the importance of Telematics and has made considerable improvements over the past years, such as the implementation of a new governance mechanism. Nonetheless, it needs to be ensured that the various tools function properly.

- ▶ **User-friendliness and interoperability of Telematics could be improved**, especially related to shared access to documents.
- ▶ **The large amount of different telematics, 23 in total, could be consolidated**, which would provide both security and efficiency gains.

Looking to the future, EMA will need to ensure that it has enough and **relevant in-house expertise** to develop and maintain solutions for future challenges and mitigate the risk of being dependent on external providers. This is especially important in view of the rise in importance of big data, as the incorporation of real-world data could significantly contribute to a simplification of the system.

Through its dedicated framework for **communication**, EMA sets clear goals to achieve an effective functioning of the system. EMA has significantly increased its communication efforts since the last study. Overall, the mechanisms in place contribute to achieving the objective of making information related to marketing authorisation procedures available to the stakeholders and public as much as possible.

- ▶ An important tool in the process is the **EMA website**, which serves as an easily accessible hub of information and receives strong support (95%) from all types of stakeholders.
- ▶ EMA has also **increased its efforts to communicate publicly**, most recently through the public hearings.

The **management of communication activities is efficient** on an operational level, and greatly facilitates the overall function of the system through easy access to information.

A minor area of improvement concerns ensuring the **large amounts of information provided** are clearly structured and categorised, to ensure transparency is not diminished by too much information.

## Potential Actions

Based on the findings of the study, a number of potential actions has been identified. Some actions would require a change in legislation. These are identified by the symbol §.

### *Functioning of the Network*

1. Organise structured exchanges between CHMP and COMP before the final decision on the indication is taken.
2. Periodically review the number and scope of the working parties, with a specific focus on temporary working parties and their status.
3. Envisage a way to reallocate CHMP's time on more critical/complex applications and innovative molecules (like for instance CAR-T CELL). For instance, confirmation through writing, adaptation of the CHMP agenda, etc.
4. Move beyond ad-hoc flexibility and develop clear strategies on how to address future challenges. This could be built by combining the efforts taken by EMA and HMAs separately.
5. Set a special focus on developing big data expertise both within EMA as well as within NCAs. An effort should be made to incorporate real life data in important areas such as post-marketing authorisation monitoring.
6. Develop further multinational teams and encourage smaller Member States to take a role in MNATs to ensure their integration despite the capacity constraints they might naturally face.

### *Adequacy of the system*

7. Create a task force to consider potential solutions to address the rising importance of combination products (i.e. develop guidelines). This can be built on the recently launched public consultation by EMA.
8. Develop coordination between NCAs/EMA and HTA bodies as much as possible. This can be done by building on existing initiatives such as EUnetHTA and expanding and promoting cooperation at the national level. The proposal for a new legislation is a first step towards better coordination.
9. Formalise coordination in addressing emergency needs, building on recently launched pilot projects. Special focus should be put on the area of medicine shortages, where awareness is relatively low. A first step might be the development of best practices guidelines at a European level which could incite the Member States to cooperate more closely on the issue.
10. Publish more detailed Telematics performance indicators, similar to those published in 2014 and 2015. These could include incident resolution, data transferred between Telematics and volume of Telematics usage.
11. Build IT expertise in house by expanding the dedicated IT team. The team should develop interoperability of EMA IT systems both among each other as well as with national databases. It could furthermore address existing issues that are identified, such as the functioning of databases. When implementing larger IT projects with the help of external expertise, ensure internal expertise is involved sufficiently to guarantee the project can be successfully maintained and developed in the future.

### *Supporting procedures*

12. Introduce a 'shelf-life' for scientific guidelines, which would mean every guideline needs to be reviewed after a certain period of time. The time period should be set according to the matter discussed by the guidelines, with innovative technologies being reviewed more frequently.
13. Ensure there are no overlaps or duplication of work, making the whole process clearer for applicants. This should be undertaken through close coordination and using existing NCA mechanisms (innovation offices) in place to support any development of EMA outreach.

14. § Review the necessity of renewals, potentially reviewing the legislation similarly to the reform of the veterinary legislation.
15. § Eliminate RMPs for generic products, creating the opportunity to refer to active substance profiles in the pharmacopeia.
16. § Simplify the Variations legislation in line with the simplifications done for variations concerning veterinary medicines. This would notably include allowing MAH to make Type IA variations directly in the databases without passing via NCAs.

### ***Centralised Procedure***

17. Further increase support to SMEs during the procedure through the creation of a mechanism similar to PRIME for SMEs. The mechanism should at the same time take into account the reservations shown by the Ombudsman inquiry.
18. Further formalise selection criteria that are currently based on the discretion of the chair / executive director to allow greater transparency and predictability.
19. Review to what extent the 22-day framework for the written consultation of the Committee can be shortened, taking into account the 10-day framework which works well under the accelerated assessment. This would require some changes to the rules of procedure.
20. § Ensure the shortcomings identified in European Medicines Agency and European Commission action plan on paediatrics are addressed, by strengthening the role of the PDCO and its coordination with other Committees and Working Parties and improving the handling and completion of PIPs.
21. Explore to what extent procedures could be simplified by allowing companies to refer to existing documentation in the MAA.

### ***Decentralised Procedure / Mutual Recognition Procedure***

22. Create a mechanism in which scientific advice given from various Member States is coordinated; through formalised exchanges or a system in which SA is aligned before it is provided to the applicant.
23. Identify inconsistencies and increase the work towards harmonising definitions and interpretation of EU legislation across Member States and encourage Member States to align their requirements with existing guidelines.
24. § Increase the work towards harmonising definitions and categorisation of products across Member States. This could be facilitated through EMA adopting guidelines on European standards/best practices.
25. Review to what measures could be taken to ensure MRP / DCP timeline are better respected, both by NCAs and industry, through either allocating additional resources or formalising and redefining timelines.

# 1. Introduction

## 1.1. Objectives and scope

Article 86 of the Regulation (EC) No 726/2004<sup>2</sup> states that “at least every ten years, the Commission shall publish a general report on the experience acquired as a result of the operation of the procedures laid down in this Regulation [and] in Chapter 4 of Title III of Directive 2001/83/EC”. Directive 2001/83/EC<sup>3</sup> also specifies that the report to be published on the experience acquired on the basis of the procedures described in its Chapter 4 of Title III “shall propose any amendments which may be necessary to improve these procedures” and that this report shall be submitted by the Commission to the European Parliament and to the Council.

In this context, the aim of the study is to assess the extent to which the current marketing authorisation system for medicines meets the objectives laid down in the regulatory framework and ultimately support the evaluation to be published by the Commission.

More specifically, the study aims:

- ▶ **To collect available data and evidence on the operation of the centralised procedure (CP), decentralised procedure (DCP) and mutual recognition procedure (MRP)**, considering the specific scope of the study;
- ▶ **To assess the effectiveness** (achievement of objectives set by the regulatory framework) **and the efficiency** (relationship between the resources used and the changes generated, which includes an examination of the administrative and regulatory burden) of the procedures and the system in place; this has to be based on a relevant methodology for gathering and analysing data and evidence and comply with the Better Regulation Guidelines and Toolbox;
- ▶ **To summarise the results of the analysis and draw useful conclusions** based on lessons learnt from the experience acquired on the basis of the market authorisation procedures;
- ▶ **To compare the current situation with the findings of the 2010 study<sup>4</sup>** and follow-up on the implementation of the recommendations made in 2010.
- ▶ **To identify options for possible actions** that may need to be taken to eliminate any existing barriers and obstacles to optimal performance and analyse the pros and cons of each option.

In terms of geographical coverage, the study covers all **28 EU Member States** as well as the countries of the European Economic Area (EEA).

In relation to the temporal and thematic coverage, the study focuses on “the experience acquired as a result of the procedures for authorisation and monitoring of medicinal products for human use, laid down in the Regulation (EC) No 726/2004 and Chapter 4 of Title III of the Directive 2001/83/EC from 2009 to 2017”. More specifically, this includes:

- ▶ A focus on medicines for human use solely. Veterinary medicinal products are out of the scope of the study, due to the recent revision of the legislative framework as a basis for new regulations on veterinary medicines and medicated feed.

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<sup>2</sup> Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency

<sup>3</sup> Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use

<sup>4</sup> The report can be found [here](#)



- ▶ A focus on CP as well as on MRP and DCP, except for subjects that fall exclusively within the competence of the MS. This excludes purely national authorisation procedures.
- ▶ The scope explicitly does not include fees due to a separate, parallel study being conducted on this issue.
- ▶ Finally, the study will take account all relevant stakeholders, e.g. partners of the European Medicines Regulatory Network as well as pharmaceutical industry and EEA citizens.

## 1.2. Key concepts and actors

To ensure clarity it is important to define a number of key actors and concepts, as they can be interpreted differently by the several types of stakeholders involved. The brief definition of some terms presented below should be considered together with more detailed descriptions and analyses provided in chapter 2.

- **European Medicines Agency (EMA):** In this study, the European Medicines Agency or EMA refers to only the agency itself, which is located in Amsterdam, as founded in 1995 and established in its current form and name in 2004 through **Regulation (EC) No 726/2004**.
- **National Competent Authorities (NCAs):** National Competent Authorities or NCAs refer to the national authorities within the EU and EEA Member States responsible for human medicines.
- **European Medicines Regulatory Network (EMRN/the Network):** The European Medicines Regulatory Network or EMRN, also referred to in this study as the Network, describes all regulatory authorities and their respective experts responsible for the regulation and evaluation of human medicines in the EU / EEA. The term itself is not a legal concept stemming from legislation.
- ▶ **European Medicines Regulatory System (the System):** The European Medicines Regulatory System or EMRS, also referred to as the System, describes the complete interaction of legislation and authorities (EMA and NCAs) dedicated to the regulation of human medicines. As with the Network, this term is also not a legal concept stemming from legislation.

## 1.3. Study questions

Whilst this study is not an evaluation as defined by the Better Regulation Guidelines, it is nonetheless guided by study questions relating to effectiveness, impact and efficiency of the overall marketing authorisation procedures. The Study Questions are split into 5 Work Packages, as presented below.

**Table 2 Summary of Work Packages and Study Questions**

Work Package	Study Question
<b>Work Package 1: The European Medicines Regulatory Network</b>	<p>To what extent has the European Medicines Regulatory Network effectively and efficiently succeeded in supporting the overall system to ensure the protection of public health, the good functioning of the internal market and considered the challenges of enlargement and simplification?</p> <ul style="list-style-type: none"> <li>▶ <b>Q1.1:</b> Is the overall organisation clear and adequate in terms of complementarity, allocation of tasks and distribution of roles and responsibilities?</li> <li>▶ <b>Q1.2:</b> Are coordination arrangements and working methods (schedule, workload...) allowing an effective functioning of the system as a whole?</li> <li>▶ <b>Q1.3:</b> Does the system rely on adequate capacities and expertise?</li> </ul>

	<ul style="list-style-type: none"> <li>▶ <b>Q1.4:</b> To what extent is the current architecture of the regulatory network and its functioning efficient? Are resources sufficient and allocated in a way that is proportionate to the results and outputs delivered?</li> </ul>
<p><b>Work Package 2: Procedures preceding submission of Marketing Authorisation Applications</b></p>	<p>To what extent have procedures preceding submission of Marketing Authorisation Applications effectively and efficiently supported the achievement of the network regulatory objectives, especially in terms of facilitating access to MA, fostering innovation and competitiveness and ensuring patients' access to reliable medicines?</p> <ul style="list-style-type: none"> <li>▶ <b>Q2.1:</b> Do pre-submission activities answer the needs of the stakeholders and facilitate access to marketing authorisation procedures?</li> <li>▶ <b>Q2.2:</b> Do pre-submission activities support the achievement of the objectives of the EU regulatory framework for medicinal products in terms of innovation and competitiveness?</li> <li>▶ <b>Q2.3:</b> Do pre-submission activities support the achievement of the objectives of the EU regulatory framework for medicinal products in terms of quality of subsequent scientific outputs and safety for patients?</li> <li>▶ <b>Q2.4:</b> Are Pre-submission activities efficient in terms of costs (time, human resources) incurred from both the industry and the EMA network to achieve the expected output?</li> </ul>
<p><b>Work Package 3: Initial Marketing Authorisation Procedures</b></p>	<p>To what extent have initial marketing procedures effectively and efficiently supported the achievement of the network regulatory objectives, especially in terms of fostering competitiveness and ensuring patients' swift access to reliable and innovative medicines whilst allowing rationalisation and simplification of the system?</p> <ul style="list-style-type: none"> <li>▶ <b>Q3.1.</b> Are Initial Marketing procedures suitable and effective to deal with all types of applications and medicines?</li> <li>▶ <b>Q3.2.</b> Do initial marketing procedures allow a swift access to medicinal products for patients?</li> <li>▶ <b>Q3.3.</b> Do initial marketing procedures support the competitiveness of the European Pharmaceuticals sector?</li> <li>▶ <b>Q3.4.</b> Do initial marketing procedures allow the marketing of reliable products?</li> <li>▶ <b>Q3.5.</b> Have initial Marketing procedures been successful in ensuring a reasonable level of administrative burden?</li> </ul>
<p><b>Work Package 4: Post-marketing authorisation procedures</b></p>	<p>To what extent have Post-Marketing Authorisation procedures effectively and efficiently contributed to improve the level of health protection of EU citizens?</p> <ul style="list-style-type: none"> <li>▶ <b>Q4.1:</b> To what extent are post-marketing authorisation procedures effectively applied and mutually complementary?</li> <li>▶ <b>Q4.2:</b> Do post-marketing authorisation procedures contribute to a higher degree of health protection for EU citizens and affect product complexity?</li> <li>▶ <b>Q4.3:</b> To what extent are post-marketing authorisation procedures</li> </ul>



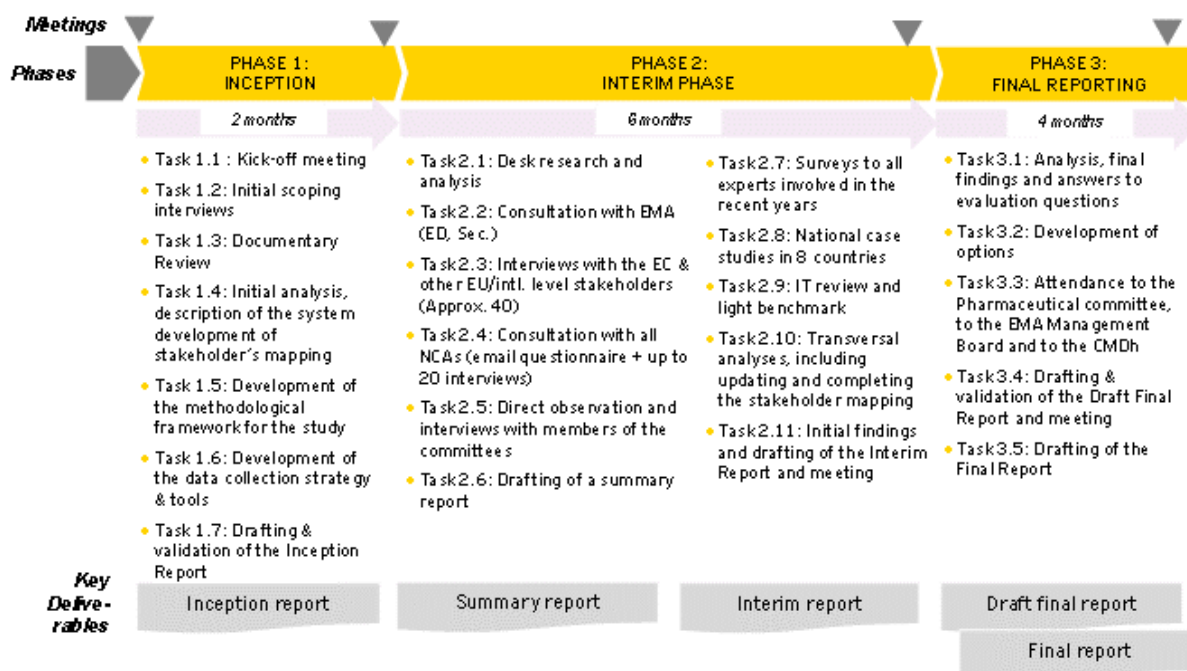
	efficient? Do they avoid any unnecessary administrative burden?
<b>Work Package 5: Support activities</b>	To what extent have support activities effectively and efficiently succeeded in supporting the regulatory network’s core activities?
	▶ <b>Q5.1:</b> Are telematics contributing to an effective functioning of the whole system?
	▶ <b>Q5.2:</b> Are telematics contributing to an efficient functioning of the whole system?
	▶ <b>Q5.3:</b> Are the communication activities contributing to an effective functioning of the whole system?
	▶ <b>Q5.4:</b> Are the communication activities contributing to an efficient functioning of the whole system?

## 1.4. Methodological approach

### 1.4.1. Overview of the methodological approach

The study was divided into three phases as presented in the figure below.

**Figure 1 Methodology for the assignment**



### 1.4.2. Overview of evidence collection

A strong emphasis has been put on collecting data and gathering the perception and input of all types of stakeholders involved in the system. For this, a number of different tools were used. The table below provides an overview of each of the tools used, including their target stakeholders and a description of what was achieved. A more detailed description of each of the tools can be found in the Annex.

**Table 3 Summary of Work undertaken to date**

Data Collection Tool	Target Stakeholders	Description
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<p><b>Interviews with EMA</b></p>	<ul style="list-style-type: none"> <li>- EMA</li> </ul>	<p>Group interviews were held with the EMA Secretariat in London. Interviews were held for each Work Package with each group interview consisting of 5 individuals.</p>
<p><b>Interviews with stakeholders at EU and international level</b></p>	<ul style="list-style-type: none"> <li>- EC</li> <li>- EU-level umbrella organisations</li> <li>- International organisation</li> <li>- Other agencies</li> </ul>	<p>The study team completed interviews with all stakeholder groups foreseen for the Study.</p> <p>The following interviews were undertaken:</p> <ul style="list-style-type: none"> <li>▶ European Commission (10)</li> <li>▶ European Parliament (1)</li> <li>▶ Umbrella Organisations (9)</li> </ul>
<p><b>Online Survey<sup>5</sup></b></p>	<ul style="list-style-type: none"> <li>- Member of EMA committees and Working Parties</li> </ul>	<p>The survey consisted of both closed and open questions and was left open for 3 weeks in March 2019. 288 experts responded.</p>
<p><b>Written Questionnaires</b></p>	<ul style="list-style-type: none"> <li>- NCAs</li> </ul>	<p>The written questionnaires were sent to all NCAs, with 22 NCAs responding. Following the receipt of written responses, interviews were held with Spain and Sweden.</p>
<p><b>Direct Observation</b></p>	<ul style="list-style-type: none"> <li>- EMA Committees</li> </ul>	<p>The study team participated in the meetings of 2 Committees: CHMP, and CMDh.</p>
<p><b>Documentary Review</b></p>		<p>Documentary review included the analysis of the relevant EMA annual reports as well as other supporting documentation.</p>

<sup>5</sup> The online survey sent to experts consisted of both closed and open questions. In fact, most closed questions were followed by an open question, where experts could, if they wished to do so, elaborate on the answer they chose in the open question. The open questions were not mandatory, as opposed to the closed ones, so as to not discourage respondents from completing the survey. When this report makes reference to answers in open questions, it quantifies the number of experts which have pointed out similar issues (e.g. 5 experts in the open questions responded that...). As not all experts responded to all open questions, the number quoted (5 in the example provided), should not be considered against the total number of respondents (288), but rather take certain specificities into account. Firstly, only a limited number of people respond to any open question. Secondly, open questions do not necessarily require a response on a specific issue, but rather invite experts to comment according to their preferences. Hence, if issue A is raised by expert 1 and issue B by experts 2, this does not necessarily mean that expert 1 disagrees with issue B or vice versa. It could simply mean the issue had not come to mind or, pressed for time, the expert had chosen to focus on a single issue. Lastly, the experts consulted were involved in different field of EMA activity, hence issues specific to one area may not be evident to all experts. In methodological terms, this means that responses brought forth by a small number of experts should not be discounted as a minority position. Rather, if such a small group of experts is quoted by the study team, this was done so after careful consideration of the circumstances, the quality and the reasonability of the open responses as well as the triangulation work with other potential evidence available.

<b>Member States Case Studies</b>	<ul style="list-style-type: none"> <li>- 8 Member States</li> </ul>	During the case studies, interviews were conducted with the NCA(s) as well as patient and industry organisations. For these Case Studies, interviews were held with 3 to 10 people for each Member State.
<b>Product Case Studies</b>	<ul style="list-style-type: none"> <li>- 20 products</li> </ul>	Product case studies looked at 22 products in detail, 15 related to the CP and 8 related to the MRP / DCP. Work consisted of documentary review.

## 1.5. Limitations of the study

During the implementation of the study, the team had to deal with certain limitations. The table below presents these limitations as well as the measures the study team took to address them.

**Table 4: Limitations of the study**

Limitation	Description	Mitigation
<b>No interviews with international regulators</b>	No interviews were conducted with US and Japan regulators due to both scheduling difficulties/lack of responses to initial contact.	The team focused on quantitative data to compare the regulatory setting on an international level. This data was readily available in scientific literature and is used throughout the report and triangulated with the feedback from EU stakeholders.
<b>Limited number of interviewed stakeholders for some Member State analysis</b>	The study team encountered difficulties in organising some case studies due to no response from the Member States. This required the selection of substitute MS at a later stage. The delay led to some case studies having fewer interviewed stakeholders than others.	The team made sure to conduct the interviews that were scheduled as thorough as possible. Where information was missing, the study team relied on findings from case studies in similar Member States as well as from feedback from EU-level actors to describe the relevant issue.
<b>No direct interviews with SMEs</b>	The study team was not able to conduct interviews directly with SMEs active in the pharmaceutical sector, as it was difficult to identify the relevant interview partners.	The study team conducted various interviews with members of research-based pharmaceutical companies through their respective umbrella organisations. As they face similar challenges as SMEs, some conclusions on the issue could be drawn.
<b>Evolving regulatory and technical landscape</b>	The regulatory, scientific and technical environment in which this study took place is constantly evolving, and the nature and diversity of actors involved inevitably means that some areas have been analysed more thoroughly than others.	Considering the scope of the study, emphasis is put on areas that were considered as key topics or priorities by the stakeholders to answer to the study questions.

## 1.6. Content of the present report

This report presents detailed answers and conclusions to each study questions. The sections are organised according to the following structure:

- ▶ Legislative background and context
- ▶ Work Package 1: The European Medicines Regulatory Network
- ▶ Work Package 2: Procedures preceding submission of marketing authorisation applications
- ▶ Work Package 3: Initial Marketing Authorisation Procedures
- ▶ Work Package 4: Post-Marketing Authorisation Procedures
- ▶ Work Package 5: Support Activities
- ▶ Overall Conclusions
- ▶ Possible Actions
- ▶ Annexes

## 2. Legislative background and context

### 2.1. Regulatory Basis

Based on Article 168 of the Treaty on the Functioning of the European Union, the European Union is given the mandate to ensure a “*high level of human health protection [through] the definition and implementation of all Union policies and activities*”. In addition, Article 168 (2) states that “*Member States shall, in liaison with the Commission, coordinate among themselves their policies and programmes (...). The Commission may, in close contact with the Member States, take any useful initiative aiming at the establishment of guidelines and indicators, the organisation of exchange of best practice, and the preparation of the necessary elements for periodic monitoring and evaluation*”.

The first efforts at the EU level in this area were formalised by Council Directive 65/65/EEC<sup>6</sup>, which first established the fundamental principle that every medicinal product placed on a Member State’s market must have been granted a marketing authorisation (MA). This concept has been further developed with the adoption of Regulation 2309/93/EEC<sup>7</sup>. Article 3 stated that “*No medicinal product referred to in Part A of the Annex may be placed on the market within the Community unless a marketing authorization has been granted by the Community in accordance with the provisions of this Regulation*”.

It is currently enshrined through two main instruments of the legal framework: the previously mentioned Regulation (EC) No 726/2004 which repealed Regulation 2309/93/EC and Directive 2001/83/EC, which repealed Directive 65/65/EEC. The two EU regulatory documents stipulate that for a medicinal product to be placed on the European market, it must hold an MA issued by a competent authority. This can be done via the Centralised Procedure (CP), according to Regulation (EC) No 726/2004; the Decentralised Procedure (DCP), or the Mutual Recognition Procedure (MRP), according to Directive 2001/83/EC; or a purely national procedure. Whilst the latter one is outside the scope of the study, the other three are described in more detail in the following sections.

#### 2.1.1. Objectives of the regulatory framework

The two previously mentioned legal documents, together with other complementary legislation, provide the EU regulatory framework. As specified in the terms of reference of the study, the framework for medicinal products has four general objectives:

To guarantee a high level of health protection for the people of Europe, particularly by providing patients as swiftly as possible with innovative and reliable products and through increased market surveillance thanks to a strengthening of monitoring and pharmacovigilance procedures.

To complete the internal market in pharmaceutical products taking account of the implications of globalisation and to establish a regulatory and legislative framework that favours the competitiveness of the European pharmaceuticals sector.

To rationalise and simplify the system as far as possible, thus improving its overall consistency and visibility as well as the transparency of procedures and decision-making.

To meet the challenges of the enlargement of the European Union.

#### 2.1.2. The intervention logic of the regulatory framework

Based on these general objectives, a complete intervention logic can be constructed, detailing the specific objectives, inputs and outputs of the process as well as the expected results. The intervention logic of the EU regulatory framework, which is presented below, serves as a general guiding framework

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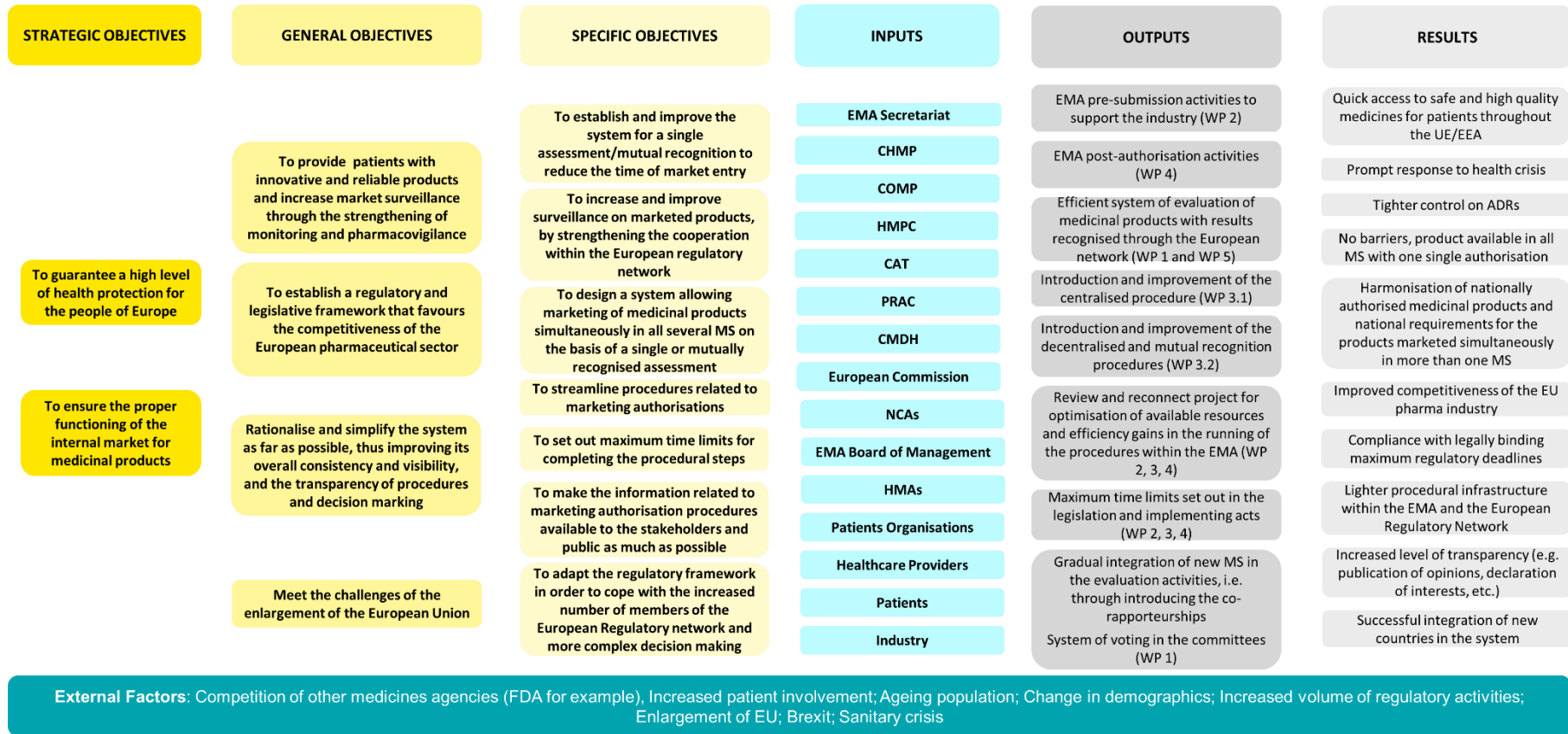
<sup>6</sup> Council Directive 65/65/EEC of 26 January 1965 on the approximation of provisions laid down by Law, Regulation or Administrative Action relating to proprietary medicinal products.

<sup>7</sup> COUNCIL REGULATION (EEC) No 2309/93 of 22 July 1993 laying down Community procedures for the authorization and supervision of medicinal products for human and veterinary use and establishing a European Agency for the Evaluation of Medicinal Product.

Study on the experience acquired as a result of the procedures for authorisation and monitoring of medicinal products for human use –Final report

when responding to the study questions related to effectiveness (achievement of objectives) and impacts (contribution of the system in meeting the strategic objectives).

**Figure 2: Intervention Logic**



## 2.2. The European Medicines Regulatory Network

The European Medicines Regulatory Network (EMRN) or “the network” is “a partnership between the European Commission, the medicines regulatory authorities in EU Member States and the European Economic Area (EEA), and the European Medicines Agency (EMA) [...] which works to ensure that patients in the EU have access to high-quality, effective and safe medicines.”<sup>8</sup>

### 2.2.1. Key actors of the network

The **European Commission** plays an important role in the regulation of medicines in the EEA. Its principal role in the European system is to take binding decisions based on the scientific recommendations delivered by EMA.

The European Commission is involved in:

- ▶ The proposal of new or amended legislation for the pharmaceutical regulation;
- ▶ The adoption of implementing measures as well as ensuring and monitoring the correct application of EU law;
- ▶ The oversight of activities of EMA;
- ▶ Ensuring appropriate collaboration with relevant international partners and promotion of the EEA system globally.

The European Commission is also directly involved in the procedures regarding product marketing authorisations. It is a key player of the network, collaborating actively with the NCAs. It is responsible for the adoption of marketing authorisations for products submitted via the centralised procedure. It is also able to take specific measures when safety issues have been identified by the Member States or through the pharmacovigilance activities.

The **European Medicines Agency (EMA)** was founded in 1995 and is a decentralised EU Agency, responsible for the scientific evaluation, supervision and safety monitoring of medicines in the EU. EMA’s mission is provided for in Regulation (EC) No 726/2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency<sup>9</sup> (hereafter Regulation (EC) No 726/2004). The Agency is responsible for ‘coordinating the existing scientific resources put at its disposal by Member States for the evaluation, supervision and pharmacovigilance of medicinal products’.<sup>10</sup> The European medicines regulatory network gives EMA access to experts from across the EU, allowing it to bring together the best-available scientific expertise in the EU for the regulation of medicines.

EMA has seven scientific committees and a number of working parties, and related groups (made up of members who have expertise in a particular scientific field) which conduct the scientific work of the Agency.

“The committee’s evaluations of marketing-authorisation applications submitted through the centralised procedure provide the basis for the authorisation of medicines in Europe.

The committees and working parties also contribute to the development of medicines and medicine regulation, by:

- providing scientific advice to companies researching and developing new medicines;
- preparing scientific guidelines and regulatory guidance to help pharmaceutical companies prepare marketing authorisation applications;

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<sup>8</sup> Brochure on the European regulatory system for medicines: “The European regulatory system for medicines A consistent approach to medicines regulation across the European Union”, 26 August 2014.

<sup>9</sup> Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency, available at <https://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2004:136:0001:0033:en:PDF>

<sup>10</sup> Article 55 of Regulation (EC) No 726/2004



- contributing to the harmonisation of regulatory requirements in the EU and internationally.”<sup>11</sup>

Each committee establishes a number of working parties at the beginning of each year mandate. The working groups consult on scientific issues relating to their particular field of expertise and are delegated certain tasks associated with the scientific evaluation of marketing authorisation applications or drafting and revision of scientific guidance documents.

Article 57(1) of Regulation (EC) No 726/2004 provides that the Agency ‘shall provide the Member States and the institutions of the Community with the best possible scientific advice on any question relating to the evaluation of the quality, safety and efficacy of medicinal products for human or veterinary use which is referred to in accordance with the provisions of Community legislation relating to medicinal products. In line with the provisions of the Regulation, the Agency is at the heart of the network, coordinating and supporting interactions between NCAs and the EC.

The key tasks of the Agency, as provided in Article 57(1) are presented in the table below.

**Table 5 Key Tasks of EMA**

Provision	Task
Article 57(1) a of Regulation (EC) No 726/2004	Coordination of the scientific evaluation of the quality, safety and efficacy of medicinal products which are subject to Community marketing authorisation procedures
Article 57(1) b of Regulation (EC) No 726/2004	Transmitting on request and making publicly available assessment reports, summaries of product characteristics, labels and package leaflets or inserts for these medicinal products
Article 57(1) c of Regulation (EC) No 726/2004	Coordinating the monitoring of medicinal products which have been authorised within the Union and providing advice on the measures necessary to ensure the safe and effective use of those medicinal products, in particular by coordinating the evaluation and implementation of pharmacovigilance obligations and systems and the monitoring of such implementation
Article 57(1) d of Regulation (EC) No 726/2004	Ensuring the collation and dissemination of information on suspected adverse reactions to medicinal products authorised in the Union by means of a database which is permanently accessible to all Member States
Article 57(1) e of Regulation (EC) No 726/2004	Assisting Member States with the rapid communication of information on pharmacovigilance concerns to healthcare professionals and coordinating the safety announcements of the national competent authorities
Article 57(1) f of Regulation (EC) No 726/2004	Distributing appropriate information on pharmacovigilance concerns to the general public, in particular by setting up and maintaining a European medicines web-portal
Article 57(1) g of Regulation (EC) No 726/2004	Advising on the maximum limits for residues of veterinary medicinal products and biocidal products used in animal husbandry which may be accepted in foodstuffs of animal origin in accordance with Regulation (EC) No 470/2009 of the European Parliament and of the Council of 6 May 2009 laying down Community procedures for the establishment of residue limits of pharmacologically active substances in foodstuffs of animal origin
Article 57(1) h of Regulation (EC) No 726/2004	Providing scientific advice on the use of antibiotics in food producing animals in order to minimise the occurrence of bacterial resistance in the Community; this advice shall be updated when needed
Article 57(1) i of Regulation	Coordinating the verification of compliance with the principles of good

<sup>11</sup> EMA website

(EC) No 726/2004	manufacturing practice, good laboratory practice, good clinical practice and the verification of compliance with pharmacovigilance obligations
Article 57(1) j of Regulation (EC) No 726/2004	Upon request, providing technical and scientific support in order to improve cooperation between the Community, its Member States, international organisations and third countries on scientific and technical issues relating to the evaluation of medicinal products, in particular in the context of discussions organised in the framework of international conferences on harmonisation
Article 57(1) k of Regulation (EC) No 726/2004	Recording the status of marketing authorisations for medicinal products granted in accordance with Community procedures
Article 57(1) l of Regulation (EC) No 726/2004	Creating a database on medicinal products, to be accessible to the general public, and ensuring that it is updated, and managed independently of pharmaceutical companies; the database shall facilitate the search for information already authorised for package leaflets; it shall include a section on medicinal products authorised for the treatment of children; the information provided to the public shall be worded in an appropriate and comprehensible manner
Article 57(1) m of Regulation (EC) No 726/2004	Assisting the Community and Member States in the provision of information to health-care professionals and the general public about medicinal products evaluated by the Agency
Article 57(1) n of Regulation (EC) No 726/2004	Advising undertakings on the conduct of the various tests and trials necessary to demonstrate the quality, safety and efficacy of medicinal products
Article 57(1) o of Regulation (EC) No 726/2004	Checking that the conditions laid down in Community legislation on medicinal products and in the marketing authorisations are observed in the case of parallel distribution of medicinal products authorised in accordance with this Regulation
Article 57(1) p of Regulation (EC) No 726/2004	Drawing up, at the Commission's request, any other scientific opinion concerning the evaluation of medicinal products or the starting materials used in the manufacture of medicinal products
Article 57(1) q of Regulation (EC) No 726/2004	With a view to the protection of public health, compilation of scientific information concerning pathogenic agents which might be used in biological warfare, including the existence of vaccines and other medicinal products available to prevent, or to treat, the effects of such agents
Article 57(1) r of Regulation (EC) No 726/2004	Coordination of the supervision of the quality of medicinal products placed on the market by requesting testing of compliance with their authorised specifications by an Official Medicines Control Laboratory or by a laboratory that a Member State has designated for that purpose
Article 57(1) s of Regulation (EC) No 726/2004	Forwarding annually to the budgetary authority any information relevant to the outcome of the evaluation procedures

The **National Competent Authorities (NCAs)** are the third important category of actors within the EMRN. There are 34 NCAs within the network, one per EU Member State and EEA country, with Germany, the Netherlands and Poland having two.<sup>12</sup> NCAs are responsible for the marketing authorisations not falling under the centralised procedures. This includes both MRP/DCP and national procedures. NCAs furthermore supply the experts that serve as members of the Scientific Committees and Working Parties of EMA.

<sup>12</sup> In Germany, there is one NCA dedicated to vaccines and biomedicines and one for all other medicines. In the Netherlands, there is one NCA for authorisation procedures, and one dedicated to pharmacovigilance. In Poland, there is one NCA for authorisation procedures, and one NCA for quality and manufacturing supervision.

The NCAs exchange and align through the so-called Heads of Medicines Agencies (HMA), which is a network of the heads of the NCAs. The HMA is coordinated by a Management Group and supported by various working groups as well as a permanent secretariat, which facilitates and supports the work of the Management Group. Based on the HMA Multiannual Work Plan<sup>13</sup>, and as far as contribution to human health is concerned, the HMA's objectives are as follows:

Ensure the availability of authorised medicinal products, especially by enhancing collaboration among Member States, by exchanging information and best practices on the management of shortages, ensuring early identification, and a rapid and harmonised evaluation and response to any new event that may potentially lead to a shortage.

Provide support in the case of Public Health Emergency issues, especially through developing the appropriate ways to rapidly communicate and share information among MS in emergency cases and new diseases status.

Confront the risks related to antimicrobial resistance, especially by implementing the European Commission Action Plan<sup>14</sup>, and by taking part in the implementation of the WHO Plan to combat antimicrobial resistance<sup>15</sup>.

Ensure timely access to new beneficial and safe medicines for patients, especially by further exploring the flexibilities offered by the EU regulatory framework to innovative medicinal products.

Promote an adequate environment for innovation and research in Europe, especially by enhancing the HMA involvement on projects related to the Innovative Medicines Initiative (IMI)<sup>16</sup>.

The presidency of the HMA is aligned with the EU presidency. HMAs meet twice during each presidency.

The European Commission, EMA and National Competent Authorities work in close collaboration with all the stakeholders involved in the development of medicines, manufacturing, provision and consumption. The figure below provides an overview of the stakeholders involved in the European Medicines Regulatory Network.

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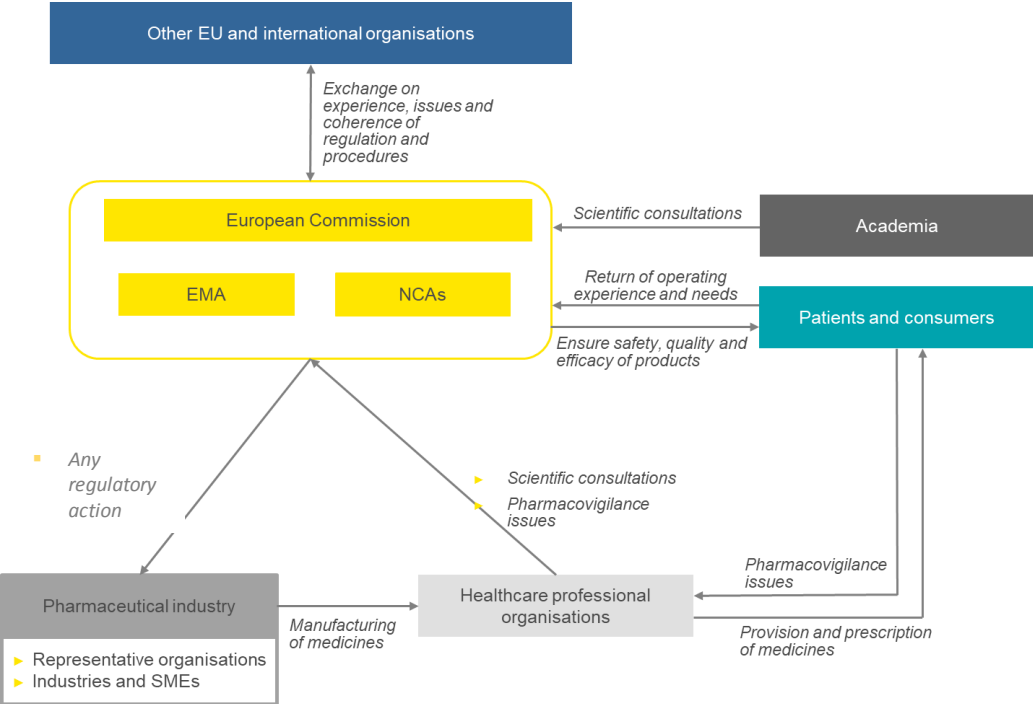
<sup>13</sup> HMA (2017). EU Medicines Agencies Network Strategy to 2020 – Heads of Medicines Agencies Multi-annual Work Plan

<sup>14</sup> European Commission (2017). A European One Health Action Plan against Antimicrobial Resistance (AMR)

<sup>15</sup> World Health Organisation (2015). Global Action Plan on Antimicrobial Resistance

<sup>16</sup> A list of ongoing IMI projects is available at: <https://www.imi.europa.eu/projects-results/project-factsheetsv>

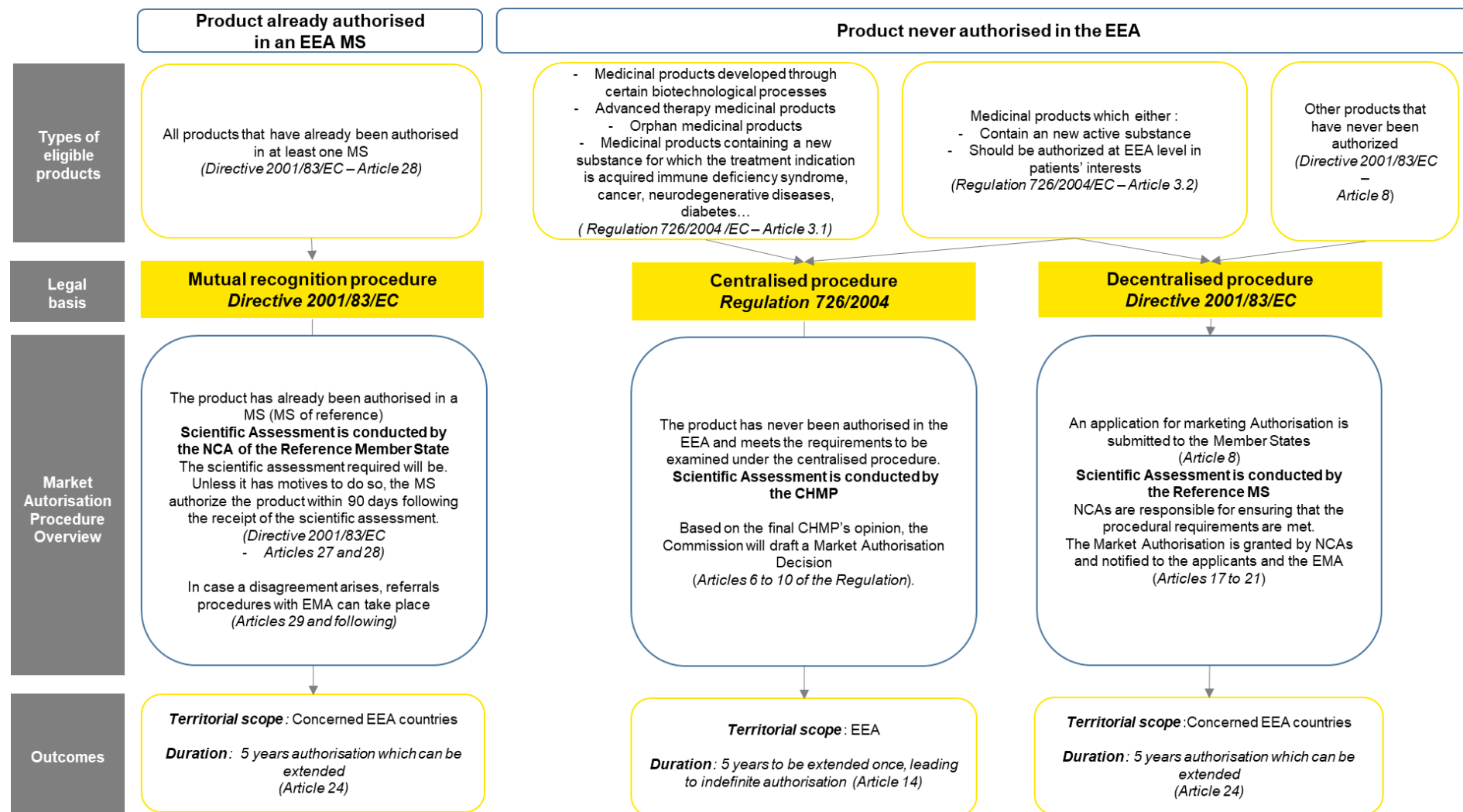
**Figure 3: Overview of the stakeholders interacted in the EMRN**



2.2.2. Activities of the Network

The main activity of the network is to contribute to the marketing authorisation process for all medicines authorised in the EEA by providing opinions and expertise towards the final authorisation decision. Apart from national authorisations in each Member State, three different procedures can be used by applicants looking to have a product authorised in Member States of the EEA. These procedures vary based on whether or not the medicinal product has already been authorised in a Member State, on the scale to which the product will be authorised at EEA level, on the type of product as well as on the involved authorities providing the required scientific assessment for the quality, efficacy and safety of the product.

**Figure 4: Overview of the available initial marketing authorisation procedures within the Regulatory Network**



Source: EY

**The rules for mutual recognition procedure and for the decentralised procedure are set in Title III, Chapter 4 of the Directive 2001/83/EC** of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use (hereafter 2001/83/EC Directive).

The rules concerning specifically the mutual recognition procedure are set out in Article 28(2) of Directive 2001/83/EC:

“Where the medicinal product has already received a marketing authorisation at the time of application, the concerned Member States shall recognise the marketing authorisation granted by the reference Member State. To this end, the marketing authorisation holder shall request the reference Member State either to prepare an assessment report on the medicinal product or, if necessary, to update any existing assessment report. The reference Member State shall prepare or update the assessment report within 90 days of receipt of a valid application. The assessment report together with the approved summary of product characteristics, labelling and package leaflet shall be sent to the concerned Member States and to the applicant”.

Only products that have already been authorised in a Member State through a national procedure are eligible for mutual recognition.

**The decentralised procedure is set by Article 28(3):**

“In cases where the medicinal product has not received a marketing authorisation at the time of application, the applicant shall request the reference Member State to prepare a draft assessment report, a draft summary of product characteristics and a draft of the labelling and package leaflet. The reference Member State shall prepare these draft documents within 120 days after receipt of a valid application and shall send them to the concerned Member States and to the applicant”.

**The process for MRP and DCP is set by Article 28 (4, 5):**

“Within 90 days of receipt of the documents referred to in paragraphs 2 and 3, the Member States concerned shall approve the assessment report, the summary of product characteristics and the labelling and package leaflet and shall inform the reference Member State accordingly. The reference Member State shall record the agreement of all parties, close the procedure and inform the applicant accordingly.

5. Each Member State in which an application has been submitted in accordance with paragraph 1 shall adopt a decision in conformity with the approved assessment report, the summary of product characteristics and the labelling and package leaflet as approved, within 30 days after acknowledgement of the agreement.”

**The centralised procedure is set by Article 3 and Annex I** of the 726/2004 Regulation. According to Article 3:

“No medicinal product appearing in the Annex may be placed on the market within the Union unless a marketing authorisation has been granted by the Union in accordance with the provisions of this Regulation.

2. Any medicinal product not appearing in the Annex may be granted a marketing authorisation by the Union in accordance with the provisions of this Regulation, if:

(a) the medicinal product contains a new active substance which, on the date of entry into force of this Regulation, was not authorised in the Union; or

(b) the applicant shows that the medicinal product constitutes a significant therapeutic, scientific or technical innovation or that the granting of authorisation in accordance with this Regulation is in the interests of patients or animal health at Union level.

The medicinal product appearing in the **Annex I** and authorised by the Union are the following:

1. Medicinal products developed by means of one of the following biotechnological processes: — recombinant DNA technology, — controlled expression of genes coding for biologically active proteins in prokaryotes and eukaryotes including transformed mammalian cells, — hybridoma and monoclonal antibody methods.

1a. Advanced therapy medicinal products as defined in Article 2 of Regulation (EC) No 1394/2007 of the European Parliament and of the Council of 13 November 2007 on advanced therapy medicinal products (1)

(...)

3. Medicinal products for human use containing a new active substance which, on the date of entry into force of this Regulation, was not authorised in the ►M7 Union ◀, for which the therapeutic indication is the treatment of any of the following diseases: — acquired immune deficiency syndrome, — cancer, — neurodegenerative disorder, — diabetes, — auto-immune diseases and other immune dysfunctions, — viral diseases.

(...)

4. Medicinal products that are designated as orphan medicinal products pursuant to Regulation (EC) No 1411/2000.”

**Table 6: Scope of the centralised procedure for human medicines**

Mandatory scope – Article 3.1	Optional scope – Article 3.2
<p>“No medicinal product appearing in the Annex may be placed on the market within the Community unless a marketing authorisation has been granted by the Community in accordance with the provisions of this Regulation.”</p> <p>The products which have to be authorised through the centralised procedure are as follows:</p> <ul style="list-style-type: none"> <li>• A medicinal product containing a new active substance to treat HIV, AIDS, cancer, diabetes, neurodegenerative diseases, auto-immune and other immune dysfunctions, viral diseases</li> <li>• medicines derived from biotechnology processes, such as genetic engineering;</li> <li>• advanced-therapy medicines, such as gene-therapy, somatic cell-therapy or tissue-engineered medicines;</li> </ul> <p>orphan medicines (medicines for rare diseases);</p>	<p>“Any medicinal product not appearing in the Annex may be granted a marketing authorisation by the Community in accordance with this Regulation [if it meets certain conditions].”</p> <p>The products which can be authorised through the centralised procedure are as follows:</p> <ul style="list-style-type: none"> <li>• A medicinal product containing a new active substance which, on the date of entry into force of the Regulation (2005), was not authorised in the Community and is not included under the mandatory scope.</li> <li>• The applicant shows that the medicinal product constitutes a significant therapeutic, scientific or technical innovation or that</li> <li>• The granting of the authorisation via the centralised procedure is in the interest of patients’ health.</li> </ul>

A more detailed overview of the three authorisation procedures can be found in the Annex.

The **initial marketing authorisation** procedures are framed by two other areas of activities where the EMRN is active:

**Activities preceding submission of marketing authorisation applications (‘Pre-submission Activities)** - scientific advice and other formalised and non-formalised support for the development of medicines and preparation of applications for marketing authorisations (Section 2.3);

**Post-Marketing Authorisation activities** - especially pharmacovigilance, referrals and variation authorisation (Section 2.5).

The following sections provide an overview of the legal background of all three areas of activity: Pre-submission, initial and post marketing authorisation activities.

## 2.3. Pre-submission procedures and activities

### 2.3.1. Pre-submission steps directly related with the implementation of the procedures for authorisation

Pre-submission procedures present an important part of the activity of the EMRN. As mentioned above, medicinal products may be authorised on the European Market via three different procedures. The pre-submission steps for these three procedures are presented below.

#### Pre-submission steps under the centralised procedure

Regulation (EC) No 726/2004 does not explicitly refer to the pre-submission steps described below. Nonetheless, it states, in its Article 6(4), that “*the Commission shall, in consultation with the Agency, Member States and interested parties, draw up a detailed guide regarding the form in which application for authorisation are to be presented.*” EMA therefore issued a Best Practice Guide<sup>17</sup>, as well as procedural advice<sup>18</sup> for applicants relying on the centralised procedure. Section 2 of the procedural advice document describes the steps prior to submitting the application.

Assessing whether a product needs to be authorised via the centralised procedure requires that the applicants are able to identify that one of the criteria is met. To support the applicants in the procedural choices that need be made prior to the actual market authorisation, EMA has set a number of pre-submission procedures.

Firstly, applicants will submit an **eligibility request**, using a standard form that has been specifically drafted by EMA. In particular, the eligibility request will allow the applicant to clearly identify the criterion under which the request for centralised assessment is presented.

EMA recommends applicants to submit the eligibility request between 7 and 18 months prior to the actual submission for authorisation. Should the eligibility request be accepted, it will become part of the applicant’s letter of intent to submit a market authorisation. Following the letter of intent, the Committee for Medicinal Products for Human Use (CHMP) and the Pharmacovigilance Risk Assessment Committee (PRAC) will appoint respective rapporteurs in charge with the scientific assessment.

As part of the pre-submission process, applicants may request a **pre-submission meeting** through a specific form drafted by EMA.

The overall objective of pre-submission meetings is to allow applicants to submit a market authorisation application which fully meets the legal and regulatory requirements. The criteria must be justified. In some specific cases, additional elements must be provided. Should the product qualify for the centralised procedure under the Advanced Therapy Medicinal Products (ATMP) criterion, a specific recommendation on classification drafted by the Committee for Advanced Therapy (CAT) should be added to the request.

#### Box 1: Pre-submission meetings

The pre-submission meetings are to take place 6 to 7 months prior to the Market Authorisation Application (MAA). Using the pre-submission meeting form, the applicant will identify a number of key elements to be discussed during the meeting. The form is to be completed by the applicant with an annex providing an overview of the product and its development programme, as well as a Draft summary of product characteristics.

After receiving the pre-submission meeting form, the product manager will review the form and assess the points to be discussed.

The Pre-submission meeting are composed of the procedure manager, along with the EMA Product

<sup>17</sup> EMA (2017). Best Practice Guide on measures improving predictability of submissions/responses and adherence to communicated submission/responses deadlines

<sup>18</sup> EMA (2018). European Medicines Agency pre-authorisation procedural advice for users of the centralised procedure



**Lead.**

EMA Quality Risk Management and the Regulatory Affairs Product Team Members will also be represented. In general, based on the nature of the product under examination, all relevant EMA staff, including CHMP and PAC members, will be present.

The meeting will be initiated by the applicant, who will make a 20 minutes presentation of the product. The various points identified in the form will then be discussed. In any case, the pre-submission meeting will not last more than 2 hours.

Once the meeting has taken place, the applicant provides EMA with meeting minutes, which are reviewed within 15 days. Overall, the drafting and comments on minutes should not last more than 30 days.

### **Pre-submission steps under the decentralised and mutual recognition procedures**

Whilst EMA has developed mechanisms in order to facilitate the submission of applications for the centralised procedure, Directive 2001/83/EC does not set such steps for the decentralised and mutual recognition procedures. Nonetheless, it should be pointed that, as stated under Articles 17 and 18 of the Directive, Member States can take measures allowing the avoidance of double-applications in various Member States.

Should a Member State note that the application is already under examination in another Member State, it may decide to suspend its procedure. The scientific assessment will be forwarded to the latter Member State once it has been completed.

In addition, under Article 18, it is stated that if the product under examination is already authorised in another Member State, that Member State may request for the Assessment Report to be forwarded. The procedure can then shift to mutual recognition; and, unless the product raises an issue, the market authorisation is to be recognised within 90 days (Refer to section 2.4.3).

#### **2.3.2. Other pre-submission activities of EMA**

EMA is implementing other pre-submission activities in order to facilitate the access to marketing authorisation procedures and support the development of medicines. These activities are independent from the procedures eventually chosen by the future applicant.

### **Scientific advice**

Based on Article 57 of Regulation (EC) No 726/2004, the Agency is responsible for providing “the Member States and the institutions of the Community with the best possible scientific advice on any question relating to the evaluation of the quality, safety and efficacy of [medicinal products].”

Regulation (EC) No 726/2004 defined scientific advice on the basis of a large scope, as it embraces questions regarding quality, clinical and non-clinical aspects of a medicinal product’s development or assessment, as well as implementation and interpretation of EU guidelines.

In order to implement its obligations with regard to scientific assistance, EMA established the Scientific Assistance Working Party (SAWP) within the CHMP.

The applicants wishing to receive scientific assistance or protocol assistance must draft a letter of intent that will be notified to the Agency’s Secretariat.

The applicant must provide a complete dossier, which will consolidate the questions submitted to advice or assistance.

In order to provide the scientific advice, a “scientific advice team” is appointed. A meeting for scientific advice can be requested, which will in particular allow applicants to receive feedbacks on the questions to be included.

### **Protocol assistance for orphan medicinal products**

Protocol assistance, on the other hand, refers to the more specific form of scientific advice to be provided to sponsors developing designated orphan medicines. The scope of protocol assistance covers

the demonstration of a significant benefit within the orphan indication, as well as clinical superiority with regard to existing medications.

### Classification and support to advanced therapy medicinal products (ATMPs)

Advanced Therapy Medicinal Products benefit from a specific set of rules laid down by Regulation (EC) No 1394/2007, which aims to subject advanced therapy to requirements likely to ensure safety as well as flexibility with regard to the rapid evolution of scientific and technological progress.

The Regulation defines Advanced Therapy Medicinal Products as either a gene therapy, a somatic cell therapy or a tissue engineered product (Article 2). Those medicinal products are subjected to a number of specific requirements. To assess whether these are properly met, a Committee for Advanced Therapy (CAT) was established (see box below – Classification of ATMPs).

To help developers establish whether the medicine they are planning to develop falls under the “ATMP” definition, for which the criteria are set under article 17, EMA has set an optional **classification procedure**.

#### Box 2: The ATMPs classification procedure

The first act of the CAT will be to appoint a CAT coordinator. The latter is responsible for drafting a scientific recommendation, which will be sent for review and comments to the Intervention Task Force (ITF – See below) and the CAT.

Whilst addressing the comments and amending the recommendation, the CAT coordinator is also able to require any additional information needed from the applicant. During the next CAT meeting, the recommendation as amended will be presented. The CAT assesses whether additional information is needed from the applicant. If not, the scientific recommendation is to the European Commission within 10 days in order to collect comments. If the European Commission formulates comments, the scientific recommendation is amended before being sent to the applicant.

As stated under the Chapter 6 of the Regulation, developers of advanced therapy medicinal products benefit from a number of incentives. The procedure is optional, and the resulting recommendation is non-binding.

### Scientific guidelines

The European Medicine Agency’s Committee for Medicinal Products for Human Use (CMDh) drafts guidelines in coordination with National Competent Authorities (NCAs) in order to provide applicants with a clear and harmonised interpretation of the EU legislation.

EMA has provided a large number of guidelines, which can be broken down as follows:

- ▶ Biological guidelines
- ▶ Clinical efficacy and safety guidelines
- ▶ Clinical pharmacology and pharmacokinetics guidelines
- ▶ ICH guidelines
- ▶ Multidisciplinary guidelines
- ▶ Non-clinical guidelines
- ▶ Quality guidelines

Applicants are invited to follow the series of guidelines, based on the concerned subject. Derivations from the indicated procedures is to be justified by applicants.

### Regulatory support for the development of medicines

#### ▶ Funding for Paediatric studies

In order to support the development of Paediatric studies and to meet the needs in terms of Paediatric medicines. To that end, the Regulation (EC) No 1901/2006 on medicinal products for Paediatric use provides under its Article 40 that:

*“1. Funds for research into medicinal products for the paediatric population shall be provided for in the Community budget in order to support studies relating to medicinal products or active substances not covered by a patent or a supplementary protection certificate.*

*2. The Community funding referred to in paragraph 1 shall be delivered through the Community Framework Programmes for Research, Technological Development and Demonstration Activities or any other Community initiatives for the funding of research”.*

Moreover, the Article 48 provides that *“The Community contribution (...) shall cover the work of the Paediatric Committee, including scientific support provided by experts, and of the Agency, including the assessment of paediatric investigation plans, scientific advice and any fee waivers provided for in this Regulation, and shall support the Agency's activities under Articles 41 and 44 of this Regulation”.*

#### ► Orphan designation

According to the Regulation (EC) No 141/2000 of the EUROPEAN PARLIAMENT and of the Council of 16 December 1999 on orphan medicinal products, an orphan designation should be accorded to medicine meeting a number of criteria:

- it must be intended for the treatment, prevention or diagnosis of a disease that is life-threatening or chronically debilitating;
- the prevalence of the condition in the EU must not be more than 5 in 10,000 or it must be unlikely that the marketing of the medicine would generate sufficient returns to justify the investment needed for its development;
- no satisfactory method of diagnosis, prevention or treatment of the condition concerned can be authorised, or, if such a method exists, the medicine must be of significant benefit to those affected by the condition.

A specific procedure is defined by EMA to analyse the orphan designation requests involving the Committee for Orphan Medicinal Products (COMP). A maximum of 90 days is required to complete the procedure. The European Commission is the final responsible for the accordance of the designation.

In order to support the development of these types of medicines, the European Commission and EMA provides eligible requestors with a number of incentives: benefit from protocol assistance, market exclusivity once the medicine is on the market and possible fee reductions.

### Other specific support for the development of medicines

#### ► PRIME Scheme

The Priority Medicines (PRIME) scheme was initiated in March 2016 by EMA. PRIME resulted from a consultation with EMA, the European Commission and the Safe and Timely Access to Medicines for Patients (STAMP). It has also mobilised the European Regulatory Network.

The eligibility criteria for PRIME are quite specific<sup>19</sup> as it is limited to medicines under development, which have not been authorised in the EEA and which are eligible under the centralised procedure for Market Authorisation. Products eligible for PRIME should be likely to **address unmet medical needs**, which means that the product presents a specific public interest in terms of either **diagnosis methods, prevention or treatment of a condition**.

In addition, products are eligible for the PRIME Scheme provided that the product demonstrates a potential to **address the unmet medical need** by maintaining and improving the public health at EU level by introducing new methods of therapy or by improving existing ones.

#### ► Quality by design

Quality by design is an approach that EMA encourages in order to ensure the quality of the medicinal products. It is aimed at ensuring that the medicinal products meet the predefined characteristics.

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<sup>19</sup> EMA (2018). European Medicine Agency Guidance for applicants seeking access to PRIME scheme

## 2.4. Initial Marketing Authorisation Procedures

The following sub-sections present the initial marketing authorisation procedures for the centralised, decentralised and mutual recognition procedures.

### 2.4.1. Centralised procedure

#### Conditions under which the centralised procedure is conducted

In accordance with article 6 (3) of Regulation 726/2004/EC, the Committee for Medicinal Products for Human Use (CHMP), will perform the scientific assessment:

“The Agency shall ensure that the opinion of the Committee for Medicinal Products for Human Use is given within 210 days after receipt of a valid application.”

The duration of the analysis of the scientific data in the file concerning the application for marketing authorisation must be at least 80 days, except in cases where the rapporteur and co-rapporteur declare that they have completed their assessment before that time.

On the basis of a duly reasoned request, the said Committee may call for the duration of the analysis of the scientific data in the file concerning the application for marketing authorisation to be extended.”

When the medicinal product under assessment contains or consists of genetically modified organisms (GMOs), the rapporteur appointed within the Committee is responsible for conducting consultations with competent authorities set at national or EU levels (Article 6 (2) of Regulation 726/2004/EC).

In particular, the CHMP is in charge of verifying that the submitted application is completed with all the requested particulars and documents. When deemed necessary, the CHMP has the ability to request that an official medicine control laboratory or a designated laboratory at national level performs tests allowing to ensure that the manufacturer’s control methods meet the level of expectation (Article 7 of Regulation 726/2004/EC).

The Committee may also request that the applicants provide additional information or undergo inspections in order to assess the manufacturer’s ability to meet the level of expectation set at EU level (Article 7 of Regulation 726/2004/EC).

The opinion of the Committee is notified to the applicant, which, within 15 days, may request in writing that the latter be re-examined within 60 days (Article 10 of Regulation 726/2004/EC).

After the final opinion has been completed and fully motivated, it is forwarded to the European Commission. If the opinion is favourable to granting the authorisation, it has to be completed with the following documents:

- ▶ A draft summary of the product characteristics
- ▶ Details of any condition or restriction which should be imposed on the supply or use of the medicinal product.
- ▶ Details on recommended conditions or restrictions with regard to the medicinal product safe and effective use.
- ▶ A proposed draft package and labelling.
- ▶ The assessment report.

The Market Authorisation decision is drafted by the European Commission. As stated under Article 10 of the Regulation, the European Commission shall draft the decision to be taken regarding the application within 15 days after the final opinion has been notified.

When preparing a draft decision that envisages granting the authorisation, the European Commission should either include or refer to the documents that complete the CHMP’s opinion. On the other hand, should the European Commission go against the Committee’s opinion, the divergence should be motivated.

Once a market authorisation has been granted via the centralised procedure, it is valid throughout the Community. As stated under Article 13, market authorisations are subjected to a number of publicity

measures: firstly, authorised medicinal products are registered in the Community Register of Medicinal Products. In addition, notification of the marketing authorisation is to be published in the EU Official Journal.

The assessment report which has been drafted by EMA is also made publicly available (European Public Assessment Reports must provide a summary which is understandable to the public and allows, in particular to comprehend the conditions of use of a medicine).

A market authorisation granted through the centralised procedure is valid for a period of five years, in accordance with Article 14. After this period has extinguished, the authorisation has to be renewed on the basis of a consolidated dossier, which is provided by the applicant. Once renewed and unless pharmacovigilance motives require additional measures to be taken, the authorisation becomes indefinitely valid. Nonetheless, should the applicant fail to place the product on the market within three years or should the product be no longer present on the market for a period of three years, the authorisation will nonetheless no longer be valid.<sup>20</sup>

### **Box 3: authorisation under exceptional circumstances**

Article 14 (8) of Regulation 726/2004/EC

“In exceptional circumstances and following consultation with the applicant, the marketing authorisation may be granted subject to certain conditions, in particular relating to the safety of the medicinal product, notification to the competent authorities of any incident relating to its use, and action to be taken. The marketing authorisation may be granted only when the applicant can show that he is unable to provide comprehensive data on the efficacy and safety of the medicinal product under normal conditions of use, for objective, verifiable reasons and must be based on one of the grounds set out in Annex I to Directive 2001/83/EC. Continuation of the marketing authorisation shall be linked to the annual reassessment of these conditions“.

### **Application submission**

The content of the application file may vary based on the nature and characteristics of the product. When applying for a Market Authorisation under the centralised procedure, the sponsors must provide all the required documentation, as listed under Article 6 of the Regulation.

Furthermore, the application has to be completed with the results of a number of tests and clinical trials as well as with a packaging mock-up and leaflet.

As stated under Article 6(2), should the medicinal product contain or consist of genetically modified organisms (GMOs), the requirements with regard to requested documents are strengthened. In particular, the application must provide an additional technical dossier as well as the results of additional investigations conducted for R&D purposes.

#### **2.4.2. Decentralised procedure**

As mentioned previously, the legal basis for the Decentralised procedure is provided for under Titre III, Chapter 4 of Directive 2001/83/EC.

### **Conditions under which the decentralised procedure is conducted**

Member States are responsible, as provided by Article 17 of the Directive 2001/83/EC, for ensuring that the procedure for granting a market authorisation in accordance with the standards set in the Directive is completed in 210 days once a complete application dossier (see above – Requested documents for application submission) has been submitted.

When assessing an application, the National Competent Authorities (NCAs) must make sure that all the requirements set by Article 8 are met. When the applicant has failed to fulfil these standards, the NCAs must be enabled by Member States based on Article 19 of the Directive to request that additional documents are provided or that testing is conducted by an official or a designated laboratory.

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<sup>20</sup> Exceptions to the sunset clause are provided under article 14§6, based on public health grounds.

Furthermore, based on Article 20, when assessing an application, NCAs should also be enabled to make sure that manufacturers and importers are capable of performing the control methods described in the application.

### **Issue of the market authorisation by the National Competent Authorities**

In accordance with Article 21, once the National Competent Authority has issued a market authorisation, it must take the necessary measures to notify the applicant as well as EMA.

Based on objective motives and verifiable reasons, the decision to issue an authorisation may be subjected by National Competent Authorities to a number of specific obligations.

### **Application submission**

As stated under Article 8 of the 2001/83/EC Directive, when an applicant wishes to obtain a marketing authorisation regardless of the centralised procedure, an application is to be submitted to the National Competent Authority (NCAs). The applicant has to be established in the EEA in order for it to be eligible under the decentralised procedure.

#### 2.4.3. Mutual recognition procedure

The legal basis for the Mutual Recognition procedure is provided for under Title III, Chapter 4 of Directive 2001/83/EC. It was set in order to allow Member States to take common decisions for the authorisation of medicinal products whilst respecting similar standards and criteria regarding the quality, safety and efficacy of the products.

### **Conditions under which the procedure is conducted**

Each Member State where an application for mutual recognition has been submitted will recognise the product based on the initially granted authorisation. This is to be performed within 90 days following the receipt of the application and the assessment report. The fact that mutual recognition has been granted is to be communicated to the applicant, the Reference Member State, EMA as well as all concerned Member States.

Articles 29 to 31 detail the procedure that has to be conducted should a disagreement arise between Member States in the context of a mutual recognition procedure.

Should a Member State consider that the product should not be authorised due to a “potential serious risk to public health” defined by Commission’s guidelines (Article 28 (2) of Directive 2001/83/EC), it should notify the applicant, the Reference Member State as well as other concerned Member States and EMA. When notifying its concerns, the Member State should detail the reasons that lead it to believe that the product should not be authorised as well as the required action that would allow for the correction of the application. Concerned Member States must make their best efforts to reach an agreement within the 90-day timeframe set for recognition. The applicant must be given the opportunity to make its point of view known, either orally or in writing.

If the Member States do not reach an agreement, a number of referral procedures can be initiated, in accordance with articles 29 and following of the Directive (See sub section 2.5.3).

### **Submission of the application**

The authorisation holder must firstly inform the Member State that granted the authorisation (Reference Member State) that an application for mutual recognition has been submitted. To this end, the applicant must notify the Reference Member State of any modification which has been brought to the initial authorisation dossier.

The National Competent Authority of the Member State which granted the marketing authorisation must prepare an assessment report regarding the product or provide an updated version of the assessment report (Article 28(2)). The Member State must provide the report within 90 days following the receipt of the request. The prepared assessment report is then forwarded to the Member States concerned by the MRP request.



For mutual recognition to be granted, the applicant must submit an application in one or more Member States. The applicant must certify whether the submitted dossier is identical to the one submitted in the Reference Member State.

Furthermore, the applicant must communicate the application to EMA, specifying Member States where an application has been submitted, as well as the dates of submission and copies of market authorisations that already have been granted. The applicant should also draw EMA's attention if the medical product is under examination for authorisation in any Member State.

#### 2.4.4. DCP and MRP

##### **CMDh**

In accordance with Article 27 of Directive 2001/83/EC, “A coordination group shall be set up for the following purposes:

- (a) the examination of any question relating to a marketing authorisation of a medicinal product in two or more Member States in accordance with the procedures laid down in Chapter 4;
- (b) the examination of questions related to the pharmacovigilance of medicinal products authorised by the Member States, in accordance with Articles 107c, 107e, 107g, 107k and 107q;
- (c) the examination of questions relating to variations of marketing authorisations granted by the Member States, in accordance with Article 35(1).

The Agency shall provide the secretariat of this coordination group.”

##### **Market Authorisation subjected to specific Obligations (Article 22 of Annex I of the Directive)**

Applications in exceptional circumstances refer to situations where the applicant is unable to provide all the required comprehensive data allowing to establish that the medicine can be used both safely and effectively under normal conditions. This inability must result from:

- ▶ The rarity of the indications for which the product is intended.
- ▶ The unavailability of comprehensive data, with regard to the state of scientific knowledge.
- ▶ The impossibility to collect the needed information due to reasons related to medical ethics.

In such cases, the market authorisation can be granted even though the above-mentioned data has not been collected, provided that at least one of the following conditions is fulfilled:

- ▶ The applicant commits to completing a studies programme within a time frame set by the NCAs. The data collected on that occasion will be included in the medicinal product's assessment via the benefit/risk profile.
- ▶ The medicinal product is only made available on medical prescription and its administration is subjected to strict medical supervision.
- ▶ The package leaflet must draw the professional's attention to the fact that certain available data concerning the product have yet to be assessed and verified.

Based on Article 24 of the Directive, the authorisation granted by the National Competent Authority under the decentralised procedure is valid for five years. The authorisation has to be renewed after five years based on a consolidated renewal application.

## 2.5. Post-authorisation procedures

### 2.5.1. Pharmacovigilance

“Pharmacovigilance rules are necessary for the protection of public health in order to prevent, detect and assess adverse reactions to medicinal products placed on the Union market, as the full safety profile of medicinal products can only be known after they have been placed on the market.”

With the adoption of Directive 2010/84/EU, the EU decided to take measures in order to improve the operation of Union law on the pharmacovigilance of medicinal products.

### **Pharmacovigilance mechanisms under the responsibility of EMA**

The pharmacovigilance mechanisms set by Regulation (EC) No 726/2004 are provided by Chapter 3 (Articles 22 to 29). The Regulation states that the provisions laid down under Article 106(1) of Directive 2001/83/EC applies to medicinal products which have been authorised via the centralised procedure.<sup>21</sup>

Firstly, the pharmacovigilance mechanisms rely on the exchange of information among the national authorities, EMA and the European Commission.

The holder of the marketing authorisation is also bound by the Regulation to respect a number of obligations regarding pharmacovigilance. In particular, the authorisation holder must designate a qualified person, who will be in charge with setting a system allowing to collect and diffuse the information about the adverse reactions which have been reported to the company. In addition, the designated expertise is responsible for drafting the reports and to generate the additional information and data which can be requested at any time by competent authorities on the grounds of a continuous assessment of the risk and benefits of the medicinal products. The designated expert is responsible for providing the information necessary to the post authorisation safety study. Should an adverse reaction be reported to the authorisation holder is due to report it to the competent authorities within Member States where such an effect has manifested. This should be done within 15 days. The holder of a marketing authorisation is to maintain detail records of all suspected adverse reactions that have been brought to its attention, in the form of periodic safety update reports. The holder must be in position to provide such a report upon request.<sup>22</sup>

**Table 7 Specific post-authorisation obligations for authorisation holders**

#### **Specific post-authorisation obligations**

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<sup>21</sup> The Article 106§1 provides that the European Commission, collaborating with the EMA and the MS, shall provide guidance with regard to the presentation, collection and verification of adverse reaction reports, as well as set technical standards to ensure that information is properly exchanged between interested parties.

<sup>22</sup> As stated under Article 24§3, periodic safety update reports must be submitted: at least every six months for the two first years following the market placement, then once a year for the following two years. Later one, the reports have to be produced on a three-year basis.



<b>Post-authorisation safety studies (PASSs)</b>	<b>Periodic safety update reports (PSURs)</b>
<p>Post-authorisation safety studies are defined under Article 1(15) of the Directive 2001/83/EC as studies “relating to an authorised medicinal product conducted with the aim of identifying, characterising or quantifying a safety-hazard, confirming the safety profile of the medicinal product, or of measuring the effectiveness of risk management measures.”</p> <p>As stated under Article 22a of the 2001/83/EC Directive, “After the granting of a marketing authorisation, the national competent authority may impose an obligation on the marketing authorisation holder:</p> <p>(a) to conduct a post-authorisation safety study if there are concerns about the risks of an authorised medicinal product. If the same concerns apply to more than one medicinal product, the national competent authority shall, following consultation with the Pharmacovigilance Risk Assessment Committee, encourage the marketing authorisation holders concerned to conduct a joint post-authorisation safety study”</p> <p>These imposed PASS are assessed by the Pharmacovigilance Risk Assessment Committee (PRAC).</p> <p>The EU post-authorisation study register allows to collect and make publicly available both the protocols for PASS as well as abstract of final studies.</p>	<p>In order to ensure that the benefit/risk assessment remains favourable after a medicine has been authorised in the EEA, the Market Authorisation Holder shall provide the competent authority with periodic safety update reports.</p> <p>According to Article 107a of the 2001/83/EC Directive, Marketing authorisation holders shall submit to the Agency periodic safety update reports containing:</p> <p>(a) summaries of data relevant to the benefits and risks of the medicinal product, including results of all studies with a consideration of their potential impact on the marketing authorisation;</p> <p>(b) a scientific evaluation of the risk-benefit balance of the medicinal product;</p> <p>(c) all data relating to the volume of sales of the medicinal product and any data in possession of the marketing authorisation holder relating to the volume of prescriptions, including an estimate of the population exposed to the medicinal product. The frequency with which the periodic safety update reports are to be submitted shall be specified in the marketing authorisation (article 107 b of the 2001/83/EC Directive).</p> <p>Based on the guidance provided by EMA<sup>23</sup>, it appears that PSURs should involve a critical examination of the information which has been collected in the interval of the MA or of the last conducted PSUR in order to identify whether new risks have appeared or whether evolutions have affected previously identified risks. Furthermore, it should summarise all the information which is necessary to conduct the benefit/risk assessment of the product. The Market Authorisation Holder is also expected to notify all the measures that have been taken to minimise the identified risks.</p>

At the national level, all relevant authorities have to set procedures allowing for the information concerning adverse reaction to be collected. In addition, systems allowing patients to notify potential adverse reaction have to be encouraged. These notifications can be collected via healthcare professionals. As stated under Article 25, when a Member State has been informed of an adverse reaction, it is bound to report to the Agency within 15 days after it has received the information. A data processing network is set by the Agency, which allows for a rapid transmission of information.

Pharmacovigilance is based on a thorough collaboration among various concerned parties. Not only are market holders, Member States and EU institutions involved, but also the Regulation states that EMA is

<sup>24</sup> Provided that the product is made available within three years. Refer to the sunset clause monitoring.

to collaborate with the World Health Organisation in order to share information with regards to measures that have been taken within the EU.

### Pharmacovigilance mechanisms undertaken at national level

Pharmacovigilance mechanisms are provided under Title IX of Directive No 2001/83/EC.

A pharmacovigilance system must be established in all Member States, allowing to collect all the useful information in order to monitor medicinal products' potential adverse reactions. The pharmacovigilance system requires that all the involved stakeholders meet certain standards.

As far as the marketing authorisation holder is concerned, it is essential that the product's sponsors designate a qualified person responsible for:

- ▶ Establishing and maintaining a system which allows for information about adverse reactions to be notified and collected
- ▶ Preparing and drafting periodic safety update reports;
- ▶ Provide the NCAs with any requested additional data or information, especially regarding the documents which are relevant to Risk/Benefit Profile.

In addition, based on Article 104 of the Directive, the Market Authorisation Holder is required to record and report suspected adverse reactions within 15 days after it has been informed.

EMA also plays a key part in pharmacovigilance mechanisms, as it is responsible, in collaboration with the European Commission and the Member States, to set a network which will allow data to be processed.

The European Commission is responsible for drafting guidance allowing to facilitate the exchange of information on adverse reactions.

#### 2.5.2. Renewals

Whether it has been granted under the centralised procedure, the decentralised or the mutual recognition procedure, the EEA Market Authorisation has a five-year validity.<sup>24</sup>

Under the **Decentralised and Mutual Recognition** Procedure, the conditions under which the renewal of the authorisation will be granted are provided for under Article 24 of the Directive 2001/83/EC.

The request for renewal must be submitted to the National Competent Authority at least three months prior to the expiry date of the authorisation.

To support the renewal the applicant must provide a consolidated dossier containing in particular elements related to pharmacovigilance. Article 104(6) states, in that respect, that periodic safety update reports must be provided at the end of the five-year validity period.

Under the **Centralised Procedure**, renewal of the authorisation lies on a re-evaluation of the product's Risk/Benefit Profile. To support the evaluation, the applicant must provide a consolidated dossier.

To that end, the applicant must submit<sup>25</sup>:

- ▶ **The administrative form for renewal.** The applicant may also include a revised summary of the product characteristics (SmPC), labelling and package or leaflet. More importantly, the renewal application must be completed with signed declarations from the applicant, stating that the quality of the product has been regularly updated and, when relevant, that the products complies with the CHMP quality guidelines.
- ▶ **Risk Management Plan (RMP):** The RMP, which was provided to support the market authorisation initial application, must be updated allowing for the product's risk/benefit profile to be continuously assessed.

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<sup>24</sup> Provided that the product is made available within three years. Refer to the sunset clause monitoring.

<sup>25</sup> EMA (2016). Guideline on the processing of renewals in the centralised procedure

- ▶ **Addendum to quality overall summary:** In particular, the addendum must contain the applicant's declaration of compliance stating that all technical and scientific profess have been taken into account to introduce the necessary changes on the product and that that all changes have been made via the variation procedure.
- ▶ **Addendum to non-clinical overview:** It consists of a critical discussion based on the non-clinical data in order to support the risk/benefit reassessment.

The reassessment procedure involves the CHMP as well as other relevant Committees such as the PRAC and the CAT.

### 2.5.3. Referrals

Referrals are specific procedures aiming to resolve issues related to the safety or benefit-risk balance of medicine or a class of medicines and concern different specific issues and disagreements between Member states as described in the table below.

A referral can be started by the European Commission, any Member States or by the company that markets the medicine. The assessment of the referral involves different actors depending on its content:

Safety-related referrals are assessed by the Pharmacovigilance Risk Assessment Committee (PRAC) and then either by the Committee for Medicinal Products for Human Use (CHMP) or by the Coordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh) for nationally authorised medicines;

All other referrals on human medicines are assessed by the CHMP only.

**Table 8: Overview of the different types of referrals**

Type of referral	Legal basis	MA Procedure concerned	Description	Possible Initiators
Safety issues	Article 107(i) to 107(k) of Directive 2001/83/EC	All	It applies when a Member State or the European Commission considers that urgent action is necessary because of safety issue (suspension or revocation of a marketing authorisation, prohibition of supply of a medicine, refusing of a renewal or in result of the evaluation of data from pharmacovigilance activities).	NCA EC
Safety, quality, manufacturing or efficacy issues	Article 20 of Regulation (EC) No 726/2004	Centralised	Pharmacovigilance procedure This procedure may be initiated as a result of the evaluation of data relating to pharmacovigilance of medicinal products  Non-pharmacovigilance procedure This procedure may be initiated in case a Member State (MS) or the European Commission (EC) considers that one of the measures envisaged under title IX (Pharmacovigilance) or XI (Supervision and sanctions) of Directive 2001/83/EC must be applied for centrally authorised medicinal products, as a result of the evaluation of data that do not relate to pharmacovigilance, for example data relating to the quality or efficacy of a the product.	EC

Type of referral	Legal basis	MA Procedure concerned	Description	Possible Initiators
	Article 31 of Directive 2001/83/EC	Decentralised and Mutual recognition	<p>Pharmacovigilance procedure</p> <p>This procedure should be initiated where the interests of the Union are involved and as a result of the evaluation of data relating to pharmacovigilance activities of an authorised medicinal product(s), and when none of the criteria listed in Article 107i(1) of Directive 2001/83/EC are met</p> <p>Non-pharmacovigilance procedure</p> <p>This procedure should be initiated where the interests of the Union are involved as a result from the evaluation of data that do not relate to pharmacovigilance activities, for example data relating to the quality and/or efficacy of an authorised medicinal product(s) or application(s).</p>	NCA EC MAH / applicant
Paediatric medicine issues	Article 29 of Regulation (EC) No 1901/2006	Decentralised and Mutual Recognition	This procedure applies when a Market Authorisation Holder applies for either a new indication, a new pharmaceutical form or new route of administration for a product authorised via the decentralised or mutual recognition procedure, provided that the above-mentioned indication, form or route makes the product suitable for children.	RMS
Harmonisation, mutual recognition procedure and decentralised procedure	Article 13(1) of Regulation (EC) No 1234/2008	Decentralised and Mutual recognition	It applies when a disagreement occurred between MS on a type II variation (potential serious risk to public health) for a medicine that has been authorised by mutual recognition or via the decentralised procedure.	RMS
	Article 29(4) of Directive 2001/83/EC	Decentralised and Mutual recognition	It applies when, during the co-ordination group procedure of Article 29(1) to (3) of Directive 2001/83/EC, the Member States fail to reach an agreement on an application for mutual recognition of a marketing authorisation or on an application in the decentralised procedure, on the grounds of a potential serious risk to public health.	RMS
	Article 30 of Directive 2001/83/EC	Decentralised and Mutual recognition	It applies when divergent decisions have been adopted by the Member States (MSs) concerning the authorisation of a nationally authorised medicinal product, in order to promote harmonisation of authorisations. It also applies when divergent decisions have been adopted by MSs concerning the suspension or revocation of a medicinal product.	NCA EC MAH

In accordance with the Article 5(3) of the Regulation (EC) No 726/2004, the Committee for Medicinal Products for Human Use shall also draw up an opinion on any scientific matter concerning the evaluation of medicinal products for human use on the request of the Executive Director of the Agency or the European Commission. The Committee shall also formulate an opinion when there is a disagreement between Member States in the evaluation of medicinal products through the mutual recognition procedure.

#### 2.5.4. Variations

Classification and conditions under which requests for variations are submitted are laid down in Commission Regulation (EC) No 1234/2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary products.

The Regulation distinguishes various types of variations:

- ▶ Minor variations of type IA refer to variations that only have no or minimal impact on the quality, safety or efficacy of the medicinal product.
- ▶ Major variations of type II refer to variations which are not extensions, and which may have a significant impact on the quality, safety and efficacy of the medicinal product.
- ▶ Minor variations of type IB refer to variations which neither fall under the definition of minor variation of type IA nor under the definition of major variation of type II.

#### **Box 4: Elements to be submitted for variations applications (Annex IV)**

When submitting an application for variations, the applicant is required to provide the following documents:

- ▶ A list of all marketing authorisations that are affected by the notification or application for variation.
- ▶ For variations of type IA, the date of implementation for each variation; for variations of type IA which do not require immediate notification, a description of all minor variations of type IA made in the last 12 months and which have not yet been notified.
- ▶ In the case where a variation should lead to other variations on the same marketing authorisations, a description of the relation between variations must be provided.
- ▶ For variations under the centralised procedure, the relevant fee payable to the European Agency.
- ▶ For variations under the decentralised and mutual recognition procedures, the list of concerned Member State as well as information regarding the Reference Member State must be provided. The relevant fees as applicable in accordance with the national rules applicable in the concerned Member States must also be provided.

#### **Variations under the centralised procedure**

Variations to the centralised marketing authorisations are subjected to Article 14 and following of the Commission Regulation No 1324/2008.

##### ▶ **Notification procedures for minor variations (Articles 14 and 15)**

As far as minor variations of type IA are concerned, the market authorisation holder must submit to the Agency a notification that contains the documents listed in Annex IV (see above). Unless the variation requires immediate notification for continuous supervision of the medicinal product, the submission of the notification can occur up to 12 months after the implementation of the variation.

Within 30 days the Agency will take measures allowing to assess the notification (see below).

Minor variations of type IB are subjected to Article 15 for notification. Once the applicant has provided the documents required under the Annex IV, the Agency must acknowledge the receipt of a valid application. Unless an unfavourable opinion has been issued within 30 days, the Agency's opinion is deemed favourable.

Once a favourable opinion has been issued by EMA, it will take measures to assess the notification (see below).

On the other hand, should the Agency issue an unfavourable opinion, the applicant is granted 30 days to amend the notification. Once the notification has been amended, EMA must issue a favourable opinion within 30 days.

► **Prior approval procedure for major variations of type II (Article 16)**

Once the applicant of the variation has submitted a valid application, EMA must issue an opinion within 60 days. The time frame can be extended up to 90 days in certain cases.<sup>26</sup>

Within 60 or 90 days, EMA may request the applicant to submit additional data.

In accordance with Article 9 and Article 34 of Regulation 726/2004/EC, EMA will issue an opinion on the application's validity. Within 15 days following the final opinion, the Agency will take measures allowing to assess the application (see below – Procedure closing measures).

► **Procedure closing measures**

In order for the procedure to be closed, EMA will inform the applicant and the European Commission whether the issued opinion is favourable or not. In the latter case, grounds that justify the unfavourable opinion must be laid down.

Should the opinion be favourable, EMA will inform the applicant and the European Commission of whether the variation required that the EC decision granting marketing authorisation has to be amended.

If needed and based on the proposal from EMA, the European Commission will amend its decision granting marketing authorisation.

## Variations under the decentralised and mutual recognition procedures

Variations to market authorisations that have been granted under the decentralised and under the mutual recognition procedures are subjected to Chapter II of the Commission Regulation 1234/2008/EC.

► **Notification procedure for minor variations (Articles 8 and 9)**

As far as minor variation of type IA are concerned, the market authorisation holder must submit a notification simultaneously to all concerned authorities within 12 months following the implementation of the variation. The submission must be submitted immediately if immediate notification is required with regard to continuous supervision of the medicinal product.

Within 30 days following the notification receipt, the measures to close the procedure will be taken by relevant authorities.

In terms of notification procedures, minor variations of type IB are subjected to requirements set by Article 9. The application has to be submitted simultaneously with all relevant authorities.

After consulting other concerned authorities, the national competent authorities in the Reference Member State acknowledges that the notification received is valid.

► **Prior approval for major variations of type II (Article 10)**

Once the applicant has submitted a request, the NCA of the Reference Member State acknowledge the valid application has been received. Within 60 days, the NCA must prepare an assessment report and a decision project, which will be forwarded to other competent authorities. Under certain circumstances the procedural timeframe may be reduced or extended up to 90 days.

Within 12 days following the receipt of the report and the decision, the relevant authorities of concerned Member States will recognise the decision. Should a disagreement arise based on a potential risk to human health, procedures laid under Article 29 shall apply (Please refer to Referrals).

► **Extension of marketing authorisations (Article 19)**

The changes that are regarded as altering profoundly the terms of the authorisation and therefore need to be validated through the extension procedure are listed in the Annex I of the Commission Regulation.

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<sup>26</sup> In accordance with the annex V Part 2, the timeframe can be extended to 90 days in the following case: variations concerning a change or an addition of a non-food producing target spices.



Those changes are related to either the active substance of the medicine or to its strength, pharmaceutical form or route of administration.

The extension is extended via the same requirements as those applying to the initial marketing authorisation.

Under the centralised procedure EMA has issued guidelines to support applicants through extensions procedure.<sup>27</sup>

▶ **Work sharing procedure (Article 20)**

The work sharing procedure is a procedure laid under Article 20. It allows an applicant to submit a group of Type B or a group of Type II variations, or a group of variations affecting various marketing authorisations.

The work sharing procedure does not apply to extensions.

▶ **Grouping variations**

The grouping variation procedure is set under Article 7.2 of the Variation Regulation. It allows Market authorisation holders to submit multiple IA variations affecting either one or several medicinal products.

Grouped variations must be distinguished from the workshare procedure. Although grouped variations can be subjected to the Work sharing procedure, as long as all medicinal products are affected by the same type of variations.

### 2.5.5. Sunset clause monitoring

The sunset clause is a provision contained under both Directive 2001/83/EC (Article 14) and Regulation 726/2004 (Article 24). Should the sunset clause be triggered, the marketing authorisation will cease to be valid.

The sunset clause is triggered when the product either:

- ▶ Is not placed on the market within three years after the authorisation has been granted.
- ▶ Is no longer placed on the market for three consecutive years.

It should be stressed that the marketing authorisation remains valid if at least one presentation of the existing product is placed in at least one Member State.

As far as centrally authorised products are concerned, EMA has set a sunset clause monitoring system. The Member State in which the product ceases to be available for one of the above-mentioned motives, the Marketing Authorisation Holder must report it via the Marketing status overview. The reporting table, once filled with regard to the cessation of the product's availability, must be attached to the cover letter.

EMA provided additional information, allowing applicants to determine when the three years period defined under the sunset clause starts running: it appears that the sunset clause timeframe starts running once the Market Authorisation has been granted or once the product can legally be placed on the market, based on variable applicable protection periods.

On the other hand, the sunset clause timer is interrupted whenever the product is initially placed on the market following the authorisation delivery, in at least one presentation and one Member State. In addition, a re-placement of the product on the market of a product which had temporarily stopped being available.

As stated under Article 14(6), the European Commission can grant exemptions to the application on the sunset clause, based on public health grounds.

Exemptions can be granted at various stages a medicinal product life-cycle. In particular, exemptions can be granted at the stage of Marketing Authorisation submission for medicinal products that address emergency public health related situations<sup>28</sup> as well as for antimicrobial medicinal products that address

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<sup>27</sup> EMA (2019). European Medicines Agency post-authorisation procedural advice for users of the centralised procedure

<sup>28</sup> Provided that the public health threats that the product in question addresses have been acknowledged by WHO or at EU level.



prevention or treatment of diseases caused by bio-terror agents. The latter must address an emergency public health need.

## 2.5.6. Other medical information monitoring

### Annual reassessment

The annual reassessment process applies to authorisations that have been granted under specific obligations (Refer to 2.4.2). Such marketing authorisation covers product for which the applicant is unable to provide the data required under Directive 2001/83/EC regarding the safety and quality of the product.

Under such circumstances, the continuation of the marketing authorisation is subjected to annual re-assessment, allowing to verify that the established conditions and obligations are met and fulfilled.

Regarding medicinal products which have been authorised through the centralised procedure, the annual re-assessment of the product's benefit/risk profile is conducted by the CHMP. The PRAC is systematically involved in the assessment.

Depending on the CHMP and the PRAC's appreciation, the marketing authorisation will either be maintained under similar obligations or be modified due to changed obligations. The market authorisation can also be suspended or withdrawn as a consequence of the assessment should the data provided by the market authorisation holder affect the benefit/risk profile in an unfavourable manor or should the market authorisation holder fail to fulfil the obligations set under the MA.

### Post-Authorisation Measures (PAMs)

PAMs are a number of measures that can be required by the Agency's Committee, either as the marketing authorisation procedure is being finalised or as part of the marketing authorisation follow-up procedure. These measures intervene based on various procedures when the Agency requires additional data in order to ensure the product's safety and sometimes efficacy.

Some PAMs are linked to the **specific obligations** which have been imposed on a conditional Market Authorisation or a Market Authorisation that has been granted under exceptional circumstances.

Whenever the MAH is required to provide additional data, this may be included either under the variation procedure or be part of the annual re-assessment procedure.

Nonetheless, whenever the interim results of the additional data do not impact either the product information or the description of the specific obligation, it can be presented under the PAM procedure.

PAMs can also result from **additional pharmacovigilance activities included in the RMP**. Once additional pharmacovigilance activities have been included in the Risk Management Plan, the changes made to these activities must be acted and validated through the variation procedure. Nonetheless, any additional information that does not affect either the description or characteristics of the measure can be presented as a PAM and validated through the appropriate procedure.

Some PAMs are also resulting from statutory obligations that MAH are bound to fill such as requests for the update of product information.

Finally, PAMs can result from a recommendation issued by the Agency during the assessment of a Market Authorisation Application.

The information that the applicant submits in view of these recommendations, as they are not legally binding, can be presented as a PAM.

In order to monitor PAMs, EMA keeps a record of the post authorisation measures. Should the Market Authorisation Holder fail to perform the required measure, the Agency will take necessary measures, which might involve the Committees. Should various products be concerned, a rapporteur or lead rapporteur will be designated as in charge to draft an assessment report regarding the impact of the lack of data, especially as it affects the ability to update the benefit/risk profile. The Marketing authorisation holder must be given the opportunity to present an oral explanation or to forward a letter to the committees. Should the Market Authorisation Holder fail to perform the required measure, the Agency will take necessary measures, which might involve the Committees. A rapporteur or lead rapporteur should various products be concerned will be designated an in charge to draft an assessment report

regarding the impact of the lack of data, especially as it affects the ability to update the benefit/risk profile. The Marketing authorisation holder must be given the opportunity to present an oral explanation or to forward a letter to the committees.

In order to enforce the required measures, the Agency may initiate a referral procedure as a way to modify, suspend or revoke the authorisation.

In order to enforce the required measures, the Agency may initiate a referral procedure as a way to modify, suspend or revoke the authorisation.

## 3. Work Package 1: The European Medicines Regulatory Network

The aim of this Work Package is to examine the extent to which the European Medicines Regulatory Network has effectively and efficiently succeeded in supporting the overall system to ensure the protection of public health, the good functioning of the internal market and considered the challenges of enlargement and simplification.

In detail, this section aims to answer four questions:

1. Is the overall organisation clear and adequate in terms of complementarity, allocation of tasks and distribution of roles and responsibilities?
2. Are coordination arrangements and working methods allowing an effective functioning of the system as a whole?
3. Does the system rely on adequate capacities and expertise?
4. To what extent is the current architecture of the regulatory network and its functioning efficient? Are resources sufficient and allocated in a way that is proportionate to the results and outputs delivered?

### Synthesis

**The system has increased in complexity** over the past years through notably the creation of PRAC and 19 new working parties as well as new initiatives such as PRIME, which has led to an increased number of days per meeting to cope with the higher workload.

**The system has remained overall effective and has adapted to the contextual changes and emerging needs over the past years:**

- ▶ Each actor within the network has a clear and dedicated role, recognised by all stakeholders. The Committees and Working Parties provide an adequate space and opportunity to discuss the scientific and regulatory details.
- ▶ The Commission and the Standing Committee fulfil their roles as well.
- ▶ Patient involvement across the network has increased significantly over the study period, which is perceived as a strength of the network.
- ▶ The EMA secretariat is successful in providing effective coordination arrangements and has adapted organisation and working methods in answer to the increased level of activity (+10% or above on the majority of tasks), thus contributing to a smooth functioning of the system, as shown by the achievement of performance indicators.

**A need for increased coordination was identified** related to the large amount of working parties as well as their temporary nature. Some coordination is lacking on specific tasks endorsed by both EMA and NCA on early advice and the identification of experts.

**The system has adapted to provide also the adequate expertise and capacity:** NCA and experts of some MS have increased their involvement, whilst EMA put at disposal both administrative and scientific support as needed. Concentration of rapporteurships on a few, prominent Member States has slightly decreased. Finally, scientific expertise is adequate to provide strong and credible opinions, even though not provided equally by all MS. Small MS increased their participation through MNAT.

However, in areas that are currently developing and will gain more relevance, **the availability of expertise will need to be ensured in the future.** On a scientific level, this includes most notably ATMPs and the intersection of medicines and medical devices. On an operational level this includes

big data and statistical expertise.

**The study period shows an increase in financial and human resources** put at disposal, consistent with the development of the system (including the expansion of existing initiatives such as patient involvement and efforts to increase communication and transparency, which also contributed to a rise in budget):

- ▶ The budget of EMA increased from EUR 208,4 million in 2010 to EUR 331,3 million in 2017 (+ 60% and an average annual growth of around 6,3%), in line with increase in activities and consequently in fee income (+75% of fees). Expenditures and revenues remained balanced and within the budgetary planning.
- ▶ The number of staff experienced a slight increase from 711 in 2010 to 799 in 2017 (including contract staff and seconded national experts), to deal with the addition of new activities, both stemming from new legislation, such as PRAC and self-imposed, such as PRIME.
- ▶ Across the Network, most NCAs have increased the resources allocated to EU-level activities over the study period

On an operational level, whilst the overall length of meetings is accepted by stakeholders, there exists **potential efficiency gains regarding the utilisation of IT, notably through increasing interoperability.**

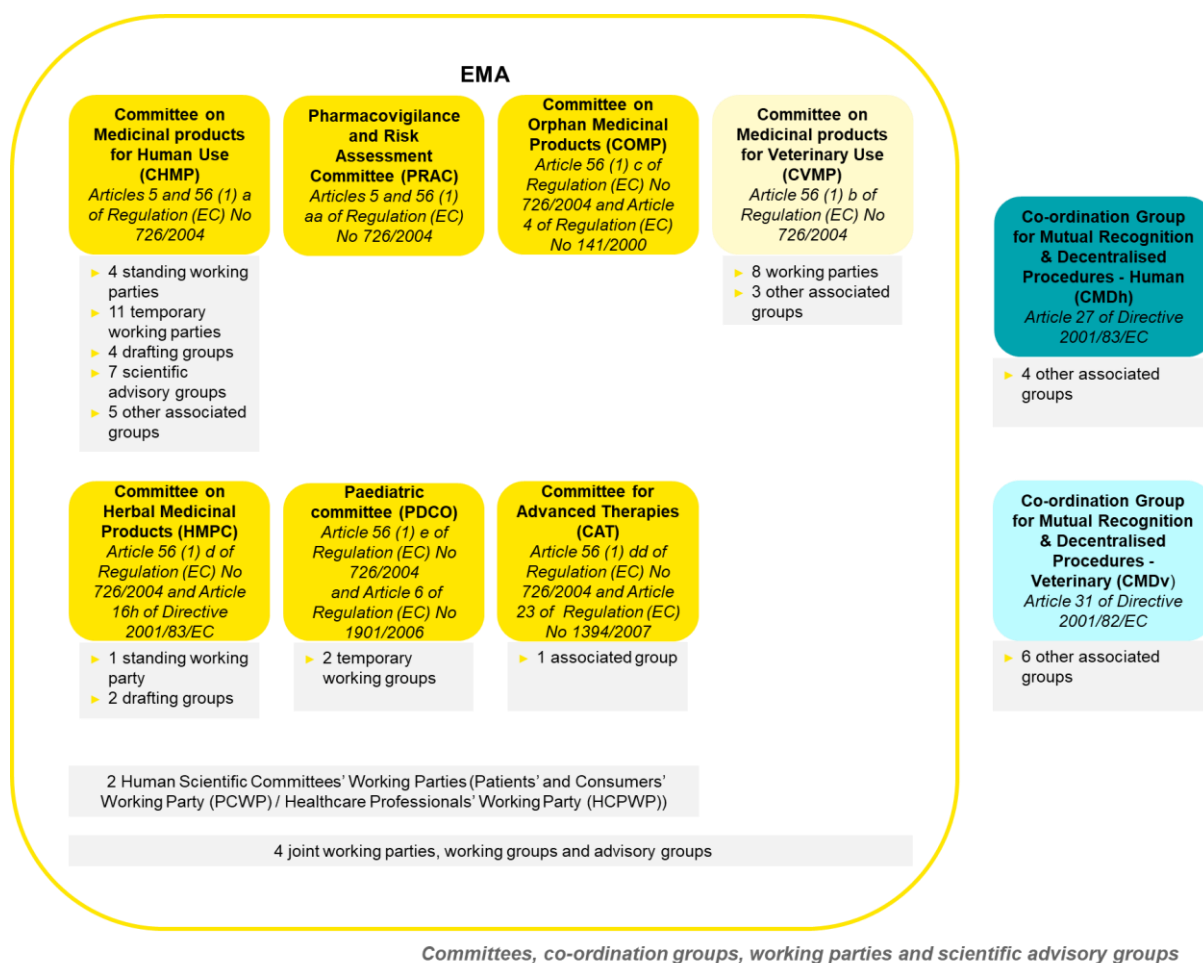
### 3.1. Is the overall organisation clear and adequate in terms of complementarity, allocation of tasks and distribution of roles and responsibilities?

3.1.1. Committees and Working Parties have increased both in number and complexity, but their roles remain clear

7 Committees and 54 Working Parties and other groups are in place within EMA, not including those associated to the CMDh. **This number has increased significantly since 2010**, when the network was composed of 6 Committees and 35 Working Parties.

- ▶ PRAC was created in 2012.
- ▶ Some Working Parties have been disbanded and others created over the period of the study.

Figure 5: Architecture of Committee structures and Working Parties and Groups<sup>29</sup>



Source: EY

The number of committees is considered as relevant to the whole system. The number of WP is more questioned.

The number of Committees, coordination groups, working parties and scientific advisory groups in place was considered as an issue in the 2010 study which concluded that whilst the creation of temporary pre-committees can contribute to an effective evaluation of medicinal products as a whole, a need exists to undertake a regular review of the 'working groups nebula' in order to lead to a 'more focused and relevant coordination workload'.

In 2019, 92% of experts agreed that the **number of committees** were appropriate, with only 8% disagreeing with this statement.

89% of experts responding to the survey considered that the number of working parties are appropriate to support the work of EMA activities. When a WP is no longer relevant or presents a duplication of work in another committee, it is disbanded after an amount of time. Although ultimately successful, the process may take some time and the adjustment of the number of Working Parties according to the actual needs may not be immediate.

- ▶ **There are currently seven Standing Working Parties, which are established permanently, that are consulted by the CHMP and other committees on scientific issues relating to their field of expertise.**

<sup>29</sup> Please note that the CVMP and CMDv are included in the figure for reasons of completeness, however they are outside the scope of this study.

Each Standing Working Party has specific rules of procedures (RoP). Standing Working Parties meet 3-6 times a year, with the exception of the SAWP, which meets 11 times a year. Standing Working Parties are relatively stable in number, with only 1 creation over the study period (the Healthcare Professionals Working Party to increase their involvement in EMA's procedures), as well as 1 disbandment (the Pharmacovigilance Working Party, which was replaced by PRAC).

▶ **Temporary Working Parties are established when work of a temporary or ad-hoc nature is required.**

These groups work on the proposals and questions regarding a specific scientific topic, as well as the drafting and revision of guidelines on this topic. Currently there are 14 Temporary Working Parties, the oldest established in 2008, the Formulation Working Group (FWG) and the Non-Clinical Working Group (NcWG), both linked to the PDCO. All other Temporary Working Parties are connected to the CHMP. The Pharmacogenomics Working Party (PGWP) is the only one governed by specific RoP; the others follow the general RoP for Temporary Working Parties. Whilst in-person meetings are limited to 3 per year, virtual meeting frequency varies greatly between 0 and 11.

The 2010 Study recommended that “various expert bodies such as working parties, scientific advisory groups and even pre-committees [...] should not be considered permanent. Whenever one of these bodies is not considered necessary any more, it should disappear.” With some Working Parties established more than 10 years ago, their ‘temporary’ nature can be questioned, with meetings being held for these parties at least two times a year.

▶ **Drafting groups are created when a process for reviewing or developing a specific guideline is adopted and none of the existing working parties cover the topic at hand.**

Currently, there exist six drafting groups, two attached to the HMPC (DG ORGAM and Q DG) whilst the other four are attached to the CHMP. The two linked to the HMPC have existed since 2004. Drafting Groups meet a maximum of 2-3 times a year in person, but some have an additional number of virtual meetings. Drafting groups are perceived as relevant.

▶ **Scientific Advisory Groups provide advice regarding the evaluation of specific types of medicines or treatments.**

There currently exist 8 SAGs of which one, the Inter-Committee Scientific Advisory Group on Oncology (IC-SAG), has specific RoP. All SAGs are linked to the CHMP with the exception of the IC-SAG, which works with all Committees except PRAC. They are demand-driven, meeting only upon request, thus confirming their relevance to address specific issues.

▶ **There are eight other groups established to provide expertise in certain areas.**

All except for the European Medicines Agency/CAT and Medical Devices' Notified Body Collaboration Group report to the CHMP. These groups provide expertise in their respective area when necessary. They do not meet often. A number of them have not published publicly available workplans recently, raising questions on their relevance.

*A table with more detailed information on the different types of Working Groups can be found in the Annex, Section 10.2, page 165.*

**The roles of Committees and Working Parties are generally clear**

The roles of Committees are clearly defined, with each committee fulfilling a dedicated role. The mandate of the committees is clarified through the RoPs, whilst their work is outlined in their respective work plans. The same holds for Standing Working Parties. Other Groups do not necessarily have dedicated RoPs, but their role within the network is nonetheless clearly outlined by the generic RoPs for different types of groups as well as their work plans. The role is further detailed clearly on the EMA website, which provides each group with a dedicated mandate.

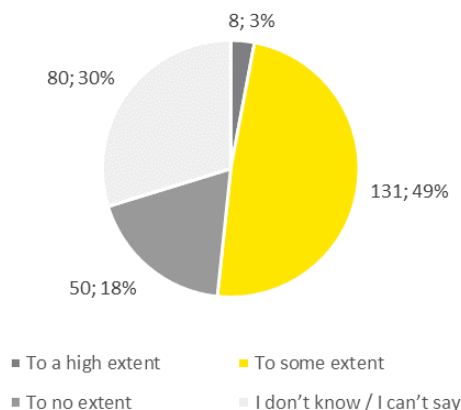
Experts responding to the online survey (86%) also considered the planning of the meetings and coordination between different entities within the network to be well-organised overall. 89% of experts responding to the online survey considered that the Chair of their respective Committees/Working Parties ensures the efficient functioning of the meetings.

**There is no Working Party that can be singled out as clearly being superfluous or greatly overlapping with another.**



A larger number of WP increases does lead to more complexity and need for coordination. 55% of experts considered overlaps to exist to a high (3%) or some extent (52%).

**Figure 6: To what extent do you consider overlaps to exist between Committees and Working Parties within EMA?**



Source: Expert Survey

However, whilst experts acknowledged that an overlap existed in some instances, they noted that this in itself does not always pose a problem. Overlaps are considered inevitable and necessary in the case of interaction between Committees and Working Parties, as the same products are subject of the discussion. Thus, overlaps do not question the particular roles of each committee and WP and their complementarity and respective added-value. The NCAs interviewed underlined this by pointing out that if an overlap leads to excessive work, it is usually addressed over the course of time. **Issues with overlaps generally arise when a lack of coordination exists.** A lack of communication and interaction can lead to synergies not being exploited. This in turn can result in expert opinions not being presented adequately and ultimately different groups reaching diverging opinions.

**The coordination between committees was identified as a potential source of improvement for the overall functioning of the network.**

Stakeholders consulted from the EMA Secretariat as well as the Commission indicated there is still room for improvement in this area. This view was shared by both experts and stakeholder organisations, which pointed out instances where two committees, i.e. CHMP and PRAC or CHMP and COMP published diverging opinions on the same or related issue.

- ▶ Regarding the divergence between **CHMP and PRAC**, this phenomenon occurred when the Pharmacovigilance legislation had just recently been implemented. It was due to the structure that stipulated that rapporteurs for each Committee came from a different Member State combined with the fact that communication was low, leading to different scientific approaches being implemented and scientific opinions differing. Whilst only the CHMP can adopt a binding opinion, this difference nonetheless led to insecurity for the applicant, and the need for EMA to invest additional time and resources to solve the situation. However, whilst some instances still exist, experts through the online survey and NCAs consulted through interview generally have pointed out that the system has improved on these issues. These improvements include the formalised PRAC report at every CHMP meeting for example, which has greatly improved the difference of opinion between PRAC recommendations and CHMP opinions, a fact that is corroborated by pharmaceutical umbrella organisations and NCAs.
- ▶ Looking at **COMP and CHMP**, there can be some administrative difficulties regarding orphan designation. The current process leads to work being done in parallel by CHMP and COMP. Usually, COMP designates an orphan status to a product for a distinct orphan indication early in the development process. Throughout the development, however, CHMP or other Committees sometimes recommend or impose that a product changes the originally envisioned therapeutic indication. This can lead to issues at the stage of the COMP orphan status re-evaluation during marketing authorisation, since it can happen that the new therapeutic indication no longer fits within the designated orphan indication. This in turn would lead to a loss of orphan status. Currently, measures mitigating this are being put in place, chiefly through involving COMP closer with other



Committees. However, the issue still persists in some cases. The finding was supported by around 5 experts as well as the Commission services, which pointed out that there had been communication issues previously, which led to friction in the system. However, they also noted that this had improved in recent years. Whilst the issue was not brought up directly by the research-based pharmaceutical industry, it nonetheless mentioned that the coordination necessary to properly involve COMP in the authorisation procedures added an additional layer of complexity.

**The responsibilities between the Committees and Working Parties could be clarified in some instances.**

17% of experts responding to the online survey mentioned there were difficulties in communication between different Committees and Working Parties, notably regarding the CAT and the PDCO.

- ▶ Regarding the **CAT**, there exist overlaps in its work with other Committees. With the CHMP, whilst the CAT prepares a draft opinion on each ATMP application, the final opinion remains the responsibility of the CHMP. Furthermore, the CAT can also provide scientific expertise and advice for the development of innovative medicines, an area that is also covered by the SAWP. In light of these overlaps, there still seems to be confusion among experts about the exact role of CAT. This even goes so far as to have 5 experts, both from CHMP and CAT as well as one NCA, questioning whether the CAT merited the status of Committee in its current form. They pointed out that decisions on classification were taken by the CHMP, and thus work in this area might be clearer and simpler if it were organised as a Working Party.

However, it is important that CAT keeps its committee status. **ATMPs is a field of emerging importance** where the network still lacks a sufficient number of experts. As such, it is important to maintain and strengthen this area. Due to the nature of CAT, overlaps are bound to exist and are necessary. It thus needs to be ensured that all experts are aware of the exact role of CAT and that the areas where it overlaps with other Committees are coordinated well.

- ▶ Looking at the **PDCO**, overlaps and coordination issues were identified specifically with the SAWP, which was further confirmed by a dozen experts in open responses to the online survey. They pointed out that there is a lack of communication and interaction in this area. A specific example provided is the definition of Paediatric Investigation Plans (PIP), which go into protocol details. This can lead to divergent opinions with the SAWP, specifically in the final advice letter as the two committees are not made up of the same members. In these cases, the applicant has to go back to the PDCO for a revision of the PIP, a procedure that could be avoided if interaction and alignment were increased. The parallel work of PDCO and SAWP was also highlighted by the research-based pharmaceutical industry. They pointed out the fact that there is no formal possibility to engage with the PDCO at an early stage, as well as the lack of coordination between the development of PIPs by the PDCO and the provision of scientific advice renders the system less consistent.

### 3.1.2. The role of the European Commission and Standing Committee is necessary to ensure appropriate safeguards

**The role of the European Commission is clear and acknowledged.**

Its primary role within the network is to take binding decision based on the scientific recommendations delivered by EMA. Further, the Commission's role throughout meetings of the EMA committees is to observe and identify issues at committee meetings and safeguard the overall legislative framework. NCAs and experts agreed that the role of the Commission is clear and well-interpreted, with no experts or NCAs noting any difficulties in the process.

**The Standing Committee provides an effective safeguard.**

Due to its setup as a Committee that puts the decisions of CHMP into legislation, there is a risk of the Standing Committee being perceived as a purely administrative procedure rather than effectively scrutinising the decisions of the CHMP. However, the Standing Committee was seen as a safeguarding framework for the overall regulatory process by EMA, the EC and the NCAs consulted during the case studies. Whilst Member State participation in scientific committees provides scientific advice, the Member State participation in the Standing Committee provides Member States with the opportunity to express themselves in a broader **risk management role**. At the same time, the MS representatives vary, as Ministries as stakeholders such as ministries participate in the Standing Committee. This provides them with the opportunity to bring up new issues or to re-examine the issues in place. Whilst there is a low frequency of issues arising, the Member States still acknowledge the value of the structure. The low

frequency of issues can point to the fact that the Member States have opportunities to ask questions at an earlier stage in the procedure, notably during CHMP deliberations, which leaves the Standing Committee as an instance of 'last-resort'. In this context, the fact that there are issues brought up from time to time shows that the Standing Committee serve more than a purely administrative purpose.

However, the necessity of **the 22-day framework** for the written consultation of the Committee was questioned by NCAs and experts, indicating that the period could be shortened, a viewpoint shared by representatives of the researched-based industry. The potential to shorten the framework without impacting the system is confirmed by looking at the accelerated assessment, where a period of 10 days is successfully applied.

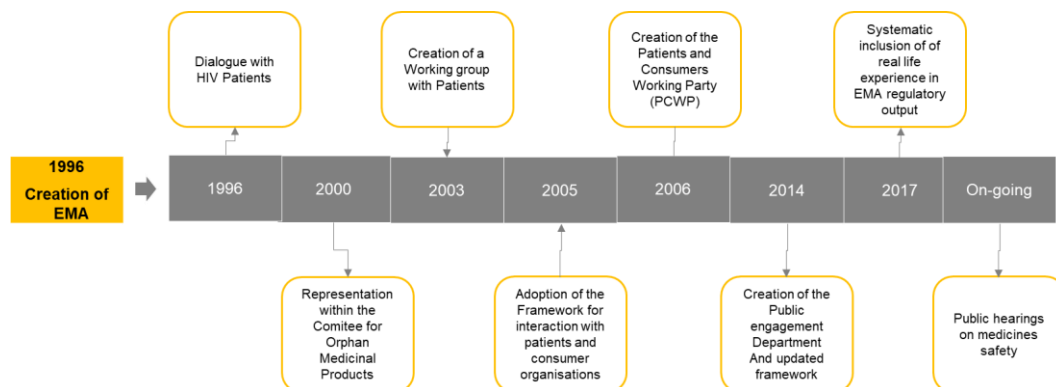
### 3.1.3. The role and representation of patients in EMA activities has increased significantly

**A key evolution in the work of the EMA network over the last 10-year period has been the increased inclusion of patient and consumer organisations in the activities of the network.**

Over the reference period, EMA has significantly increased its efforts with stakeholder engagement being a recurrent priority since 2010. The 2010 study found that a manner in which the Regulatory Network could adapt to current and future challenges was through gathering information from all stakeholders, patients included. Patients have been provided with greater opportunities for involvement.

First efforts to increase patient involvement were taken before the reference period of this study and are presented in the figure below. As of today, COMP, PDCO, CAT, and PRAC have patient involvement included in the underlying legislation. In the HMPC, patients are observers, whilst in the CHMP they provide oral explanations when required.

**Figure 7: Milestones of EMA Patient & Consumers Involvement within EMA**



Source: EY

On the road to more citizen involvement, EMA created **working groups** with patients in 2003 and adopted a **formalised framework** for interaction with patient and consumer organisations in 2005. The framework, which was revised in 2014, defines the role of patients in scientific committees and facilitates their involvement by developing training programmes and introducing daily allowances for patients.

The next major step of patient involvement was the creation of the **Patients' and Consumers Working Party (PCWP)** in 2006, which provides recommendations to human scientific committees on all matters of interest in relation to medicines.

The latest step of patient involvement was the creation of public hearings, the first of which was held in September 2017 on Pharmacovigilance measures, which aims to support EMA in its engagement with EEA citizens by creating a space to collect their views and experiences. The key objectives of the public hearings are:

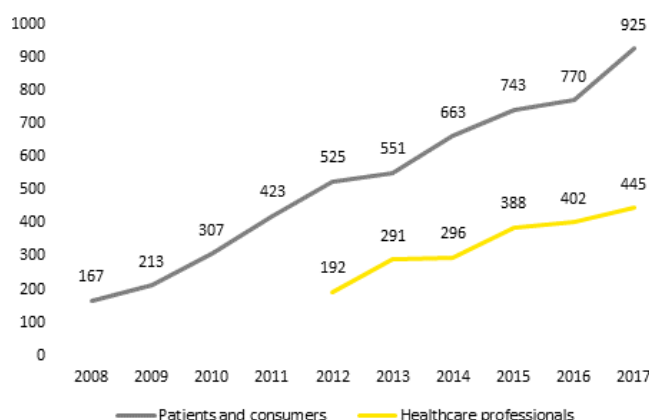
- ▶ Increasing transparency
- ▶ Empowering EEA citizens by giving them a voice in the evaluation process
- ▶ Improve the public understanding of the scientific and regulatory process
- ▶ Add value to the evaluation process beyond existing channels of stakeholder engagement

The first public hearing was held on Valproate and related substances. A second hearing was held in June 2018 on quinolone and fluoroquinolone antibiotics. These public hearings were considered by stakeholders from NCAs, patient organisations and industry as providing an important platform for patients to provide input.

**As a consequence of the growing opportunities for stakeholder involvement, the number of patients and the number of healthcare professionals (HCP) involved in EMA's activities has steadily increased.**

Patient involvement rose from 213 patients in 2009 to 925 patients representing 25 organisations in 2017.<sup>30</sup> The number of HCP involved in EMA activities evolved from 192 in 2012 to 445 in 2017, representing 29 organisations.<sup>31</sup>

**Figure 8: Overall number of patient & consumer and healthcare professional's involvement in EMA activities<sup>32</sup>**



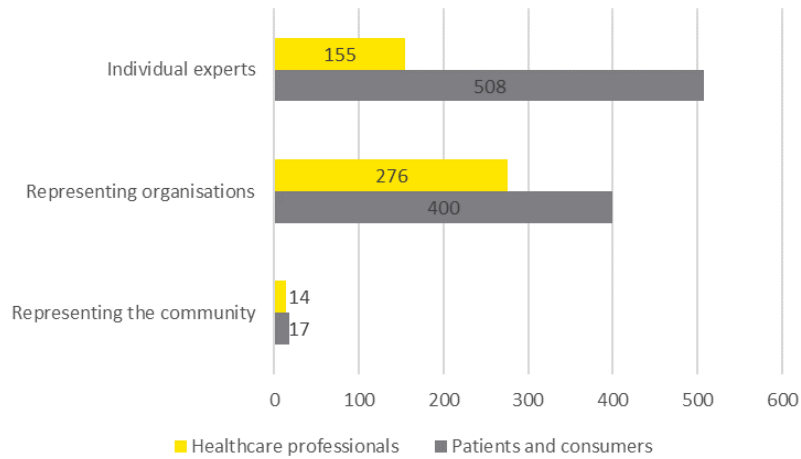
<sup>30</sup> **Patient and consumer organisations involved in 2017:** AGE Platform Europe (AGE), Alzheimer Europe (AE), Debra International, European AIDS Treatment Group (EATG), European Cancer Patient Coalition (ECPC), European Federation of Allergy and Airways Diseases Patients' Associations (EFA), European Federation of Neurological Associations (EFNA), European Foundation for the Care of Newborn Infants (EFCNI), European Gaucher Alliance (EGA), European Genetic Alliances' Network (EGAN), European Haemophilia Consortium (EHC), European Headache Alliance (EHA), European Heart Network (EHN), European Institute of Women's Health (EIWH), European Liver Patient Association (ELPA), European Multiple Sclerosis Platform (EMSP), European Network of Fibromyalgia Associations (ENFA), European Organisation for Rare Diseases (EURORDIS), European Parkinson's Disease Association (EPDA), European Patients' Forum (EPF), European Prostate Cancer Coalition (EUomo), European Public Health Alliance (EPHA), Fabry International Network (FIN), Global Alliance for Mental Illness Advocacy Networks (GAMIAN-Europe), Health Action International (HAI), International Alliance of Patients' Organizations (IAPO), International Bureau of Epilepsy (IBE), International Diabetes Federation European Region (IDF Europe), International Patient Organisation for Primary Immunodeficiencies (IPOPI), Myeloma Patients Europe (MPE), Pain Alliance Europe (PAE), Spinal Muscular Atrophy Europe (SMAE), Thalassaemia International Federation (TIF) The European Consumers' Organisation (BEUC), United Parent Projects Muscular Dystrophy (UPPMD)

<sup>31</sup> **HCP organisations involved in 2017:** European Academy of Allergy and Clinical Immunology (EAACI), European Academy of Paediatrics (EAP), European Academy of Neurology (EAN), European Association for Clinical Pharmacology and Therapeutics (EACPT), European Association of Hospital Pharmacists (EAHP), European Association for the Study of Diabetes (EASD), European Association of Urology (EAU), European College of Neuropsychopharmacology (ECNP), European Federation of Internal Medicine (EFIM), European Forum for Primary Care (EFPC), European Haematology Association (EHA), European League Against Rheumatism (EULAR), European Headache Federation (EHF), European Renal Best Practice (ERBP), European Respiratory Society (ERS), European Society of Cardiology (ESC), European Society of Endocrinology (ESE), European Society for Medical Oncology (ESMO), European Specialist Nurses Organisations (ESNO), European Society of Oncology Pharmacy (ESOP), European Society of Radiology (ESR), European Union of General Practitioners / Family physicians (UEMO), European Union Geriatric Medicine Society (EUGMS), European Working Group on Gaucher Disease (EWGGD), Health Care Without Harm Europe (HCWH Europe), International League Against Epilepsy (ILAE), Pharmaceutical Group of the European Union (PGEU), Standing Committee of European Doctors (CPME), United European Gastroenterology (UEG)

<sup>32</sup> EMA, Stakeholder Engagement Report 2017

Stakeholders were either representing organisations or intervening as individual experts in the assessment process of a product.<sup>33</sup> Whilst the majority of patients in 2017 were involved as individual experts, the majority of HCPs represented healthcare professional organisations. A detailed overview of patient involvement by area of activity can be found in the Annex.

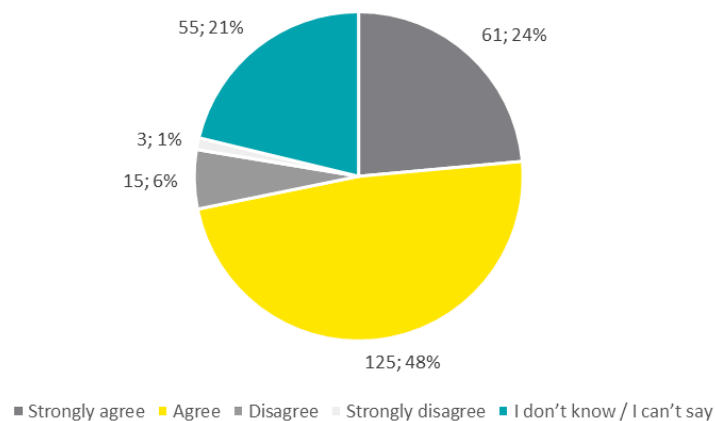
**Figure 9: Overview of involvement in EMA activities, by type of representation (2017)**<sup>34</sup>



**The institutionalisation of the patient involvement has led to a better understanding of the work from both sides**

Interviewed stakeholders agreed that EMA has undertaken large efforts to increase the engagements with patients and consumers. The institutionalisation of the patient involvement has led to a better understanding of the work from both sides. The mutual benefit is also noted by the experts consulted in the survey. As shown in the figure below, 72% of experts agree (48%) or strongly agree (24%) that patient input provides added value, and only 7% believe this is not the case.

**Figure 10: Regarding the input by patients’ organisations, to what extent do you agree that this intervention adds value to the overall work of the Network?**



Source: Expert Survey

<sup>33</sup> EMA, Stakeholder Engagement Report 2017

<sup>34</sup> EMA, Stakeholder Engagement Report 2017

### Product Case Study 1: TRESIBA

TRESIBA demonstrates the extent to which marketing authorisation procedure activities support the achievement of the objectives of the EU regulatory framework for medicinal products in terms of innovation and competitiveness.

During the Tresiba market authorisation procedure, two Healthcare Professional and Patient Organisation consultations were launched on 10 May 2012 and 10 September 2012. The organisations were consulted as to whether sufficient measures had been put in place to ensure the safe and correct use of a new high strength concentration in the drug. The Diabetes/Endocrinology Scientific Advisory Group was also asked to address questions on the benefit/risk of the new high strength concentration.

Even though the pre-submission period lasted for approximately three years, the market authorisation procedure lasted only 169 days until the CHMP assessment, which is 41 fewer days compared with the calendar provided by Article 6(3) of Regulation 726/2004. The CHMP issued a positive opinion.

This case shows that various resources and expertise are mobilized. As a result, it proves a balance between timely access for the patients to the product and adequate information on the benefits and risks of the patients; this is linked with the objective of the pilot.

#### **Whilst the study period has seen a positive trend in the involvement of patients and HCPs in the activities of the network, there are some small areas of fine-tuning.**

Firstly, whilst European level organisations are well aware of the patient involvement opportunities, this is not the case for national organisations. During national case studies, 5 of the patient organisations interviewed had little to no knowledge of procedures at the EU level. Whilst this points on first instance to difficulties in communication between European patient umbrella organisations and their national counterparts, it is also an area in which EMA could mobilise the network to raise awareness. In light of the importance of the field and the significant efforts undertaken, higher visibility would ultimately benefit the agency.

Whilst patient organisations have called for more patient involvement, the number of patients invited needs to be balanced with ensuring the relevant expertise is available. Whilst most experts agreed in the open questions to the survey that patient involvement is valuable and can clarify decisions, they noted that it often relies on the expertise of the patient. To ensure efficiency, it would thus be necessary to ensure the participating patient has the necessary expertise. A patient without the necessary expertise provides limited added value. In this regard, around a dozen responses on the expert survey, corroborated by the statements of 2 patient organisations, highlighted the importance of a thorough check of Conflict of Interest also for members of patient organisation in order to ensure their independency and their relevant expertise. The selection of patients is thus essential to ensure the process is valuable.

Lastly, whilst the selection of organisations participating in the Patients' and Consumers Working Party (PCWP) is defined, stakeholders consulted through interviews indicated that the reasons for selecting specific organisations over others were not always clear. Currently, the mandate of the PCWP stipulates that 22 of its Members are appointed by a decision of the Executive Director from amongst the list of EMA eligible organisations and 6 by the Committees (1 each). Whilst organisations can express interest, the ultimate selection is done by EMA. This means that in cases where two applicants have similar qualifications, EMA will have to make a decision. As the modalities of the decision are not public, this can lead to a lack of transparency.

#### 3.1.4. The organisation of the European Medicines Regulatory Network is clear and adequate despite some area of overlaps between EMA and NCAs regarding early scientific advice and identification of experts

#### **The overall organisation of the European Medicines Regulatory Network is clear and well-defined.**

The roles and responsibilities of the actors within the Network are clearly defined through the legislative texts, most notably Regulation (EC) No 726/2004 and Directive 2001/83/EC. The network is furthermore guided by a 5-year strategy, the latest version being the "EU Medicines Agencies Network Strategy to

2020.”<sup>35</sup> The strategy, which was developed jointly by EMA and HMA, serves as a first indicator of successful cooperation within the network.

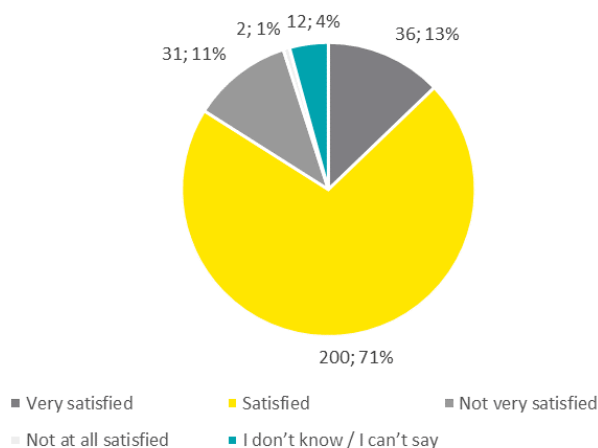
**The clarity of the organisation was confirmed by most stakeholders.**

They highlighted the complementarity of the respective roles and responsibilities of the network: 84% of experts considered the roles and responsibilities to be clear, with only 9% of respondents questioning the overall clarity of the roles and responsibilities. 78% of NCAs were also satisfied overall with the clarity of the network. Synergies were also strongly recognised by both the NCAs and experts responding to the online survey, with 95% of NCAs and 85% of experts responding considering synergies to be in place in the roles and responsibilities of the network.

**The organisation is effectively contributing to the good functioning of the Network.**

Whilst it relies on national competences and expertise, it benefits from strong coordination mechanisms, with EMA playing an effective facilitation role despite the increasing complexity of the regulatory and scientific environment. This overall statement is backed by both the feedback received from all groups of stakeholders consulted as well as the fact that EMA has successfully achieved the targets for the large majority of its activities in the past years, according to its annual activity reports.

**Figure 11: To what extent are you satisfied with the overall functioning of the Network?**



Source: Expert Survey (numbers represent number of respondents)

- ▶ 17 out of 23 respondents from National Competent Authorities considered themselves to be very satisfied with the overall functioning of the network, with none of the responding NCAs being unsatisfied with the functioning.
- ▶ This satisfaction was also reflected through the responses to the online survey by experts, with the majority of experts responding to the online survey satisfied with the overall functioning of the network. 14% of survey respondents considered themselves to be very satisfied, with 69% outlining their general satisfaction.

The overall design of the network was considered to be well-balanced and satisfying by other groups of stakeholders (such as industry and patient organisations), with each entity playing their role - the EMA Secretariat was perceived as a strong coordinator and organiser (providing technical, scientific and administrative support) with the NCAs perceived as providing scientific expertise and ensuring the scientific continuity for the EU. Stakeholders perceived this combination as unique and successful.

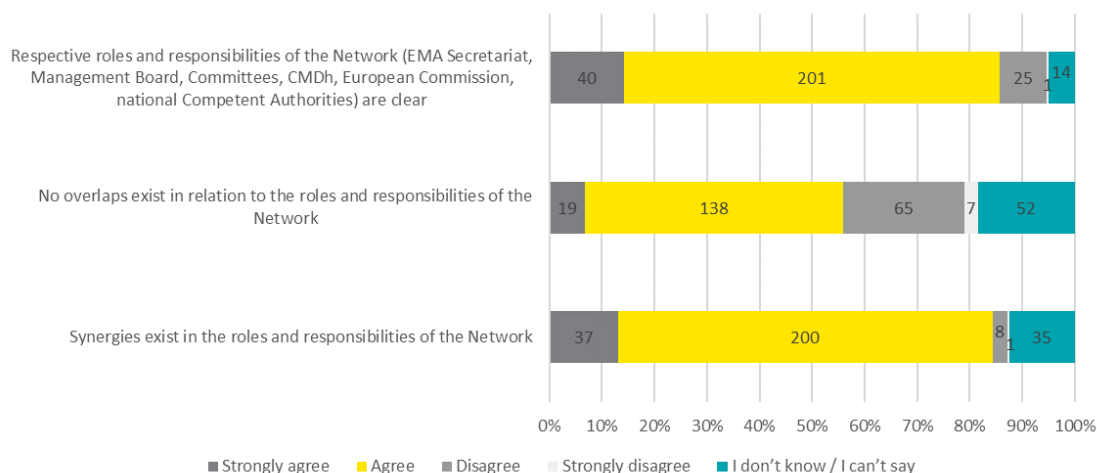
**However, a few overlaps between the activities of the EMA Secretariat and NCAs have been identified.**

This demonstrates that challenges remain in the manner in which actors are undertaking their role in practice. 17 NCAs considered that overlaps exist between the different stakeholders of the Network. Among the experts, 45% disagreed with the statement that no overlaps exist.

<sup>35</sup> Available at [https://www.ema.europa.eu/en/documents/other/eu-medicines-agencies-network-strategy-2020-working-together-improve-health\\_en.pdf](https://www.ema.europa.eu/en/documents/other/eu-medicines-agencies-network-strategy-2020-working-together-improve-health_en.pdf)



**Figure 12: To what extent do you agree with the following statements**



Source: Expert Survey

Two specific areas of overlaps were pointed out by stakeholders.

- ▶ Overlaps were identified by stakeholders from NCAs in relation to the respective roles played by the EMA Secretariat and NCAs, **particularly in relation to early advice activities**. According to the EMA Regulatory Science to 2025 strategic reflection, EMA intends to expand further its already ongoing early advice activities, especially concerning reaching out to academia and SMEs. However, this is generally an area in which NCAs are very active, as contacts are more easily formed and maintained at national level. This is confirmed by 3 NCAs interviewed during the case studies. Hence, involvement of EMA without clear coordination with NCAs and taking into account the structures already in place at national level may lead to a duplication of efforts. To ensure coordinated action and a clear procedure for the industry, any increase in EMA's activity should rely on the national structures in place.
- ▶ Another area where closer coordination between EMA and NCAs could increase the overall effectiveness of the system is the **identification of the relevant experts at national level for the expert database**. Compared to the 2010 Study, which identified the need to enhance the availability of experts and NCA involvement, the system has improved significantly overall. This is in large part due to closer cooperation between EMA and in the area. Nonetheless, it is worth to mention that during the Member State case studies, two of the interviewed NCAs noted that there can be inconsistencies between the selection of experts by EMA and the expertise identified by the NCAs. In these cases, NCAs faced difficulties in understanding the choice made by the EMA Secretariat as the NCAs would have considered another expert as more pertinent for the role. This does not mean that the chosen expert did not have the relevant credentials, but rather that NCAs would have preferred a different expert to attend the committee.

## 3.2. Are coordination arrangements and working methods allowing an effective functioning of the system as a whole?

3.2.1. The Secretariat has evolved over the study period with the Secretariat being recognised for both its administrative and scientific role

**The EMA Secretariat provides technical, scientific and administrative support for the Committees and the Working Groups and ensures appropriate coordination between them.**

The organisation of the EMA Secretariat has evolved over the study period introducing new advisory functions and support services. These changes include:



- ▶ The addition of an advisor on international affairs in 2012 to the organigramme, granting the position a higher visibility;
- ▶ A complete redesign of the organigramme of EMA in 2013, which was undertaken in the scope of the Review & Reconnect programme.

In the area of Human medicines, this led to Development and Evaluations of Human Medicines being split into two separate divisions as well as Pharmacovigilance receiving its own division, taking account of the revision of the pharmacovigilance legislation.

- ▶ Another restructuring took place in 2016, when the Procedure Management and Business Support Division was integrated into other divisions. 2016 also saw the creation of an advisor on Scientific Committees Regulatory and Science Strategy.

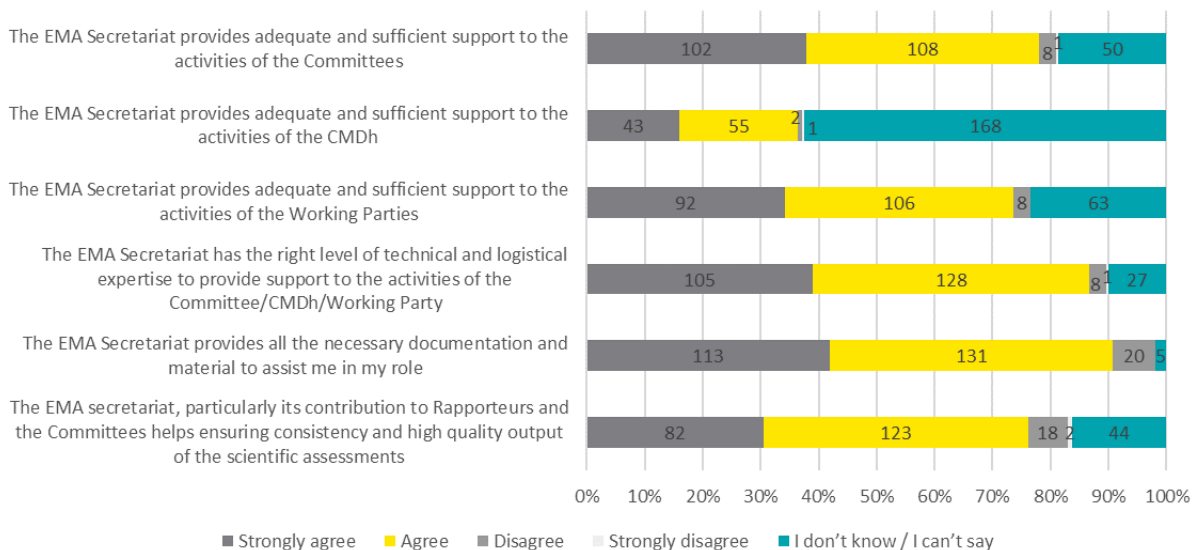
A figure presenting the evolution of the EMA organigramme can be found in the Annex, Section 10.4 page 172.

**The structure of the Secretariat is effective in providing support to the procedures.**

The 2010 study found that the work of the Secretariat was unanimously recognised as useful and efficient, with the extension of some of the Secretariat’s activities towards more scientific activities (as foreseen by the regulation) generally considered to be positive. The overall effectiveness of the Secretariat is confirmed by the present study.

Consultation with other groups of stakeholders confirmed that the Secretariat is clearly seen as facilitating the work of the network and providing support to the committees. Expert respondents to the online survey were positive with regard to the support provided by the EMA Secretariat. 81% of experts strongly agreed or agreed that the EMA Secretariat provides adequate and sufficient support to the Committees’ activities. Interviews with NCAs outlined that overall collaboration with the EMA Secretariat was well-established.

**Figure 13: With regard to the EMA Secretariat, to what extent do you agree with the following statements?**



Source: Expert Survey

Concerning the support provided by the Secretariat to the CMDh, the respondents from the online survey also considered the support to be adequate and sufficient. 88% of respondents either strongly agreed (40%) or agreed (48%) that the Secretariat has the right level of technical and logistical expertise to provide support including training to the activities of the Committees/ CMDh and Working Parties. 92% of experts responding to the survey also considered that the Secretariat provides all the necessary documentation and material to assist in their role.

During the interview with the EMA Secretariat, it was pointed out that the added value of the Secretariat was aiming to ensure an ‘institutional memory’ of the network. As such, the Secretariat ensures continuity of network activities.

3.2.2. The EMA Secretariat has been successful in organising working methods, despite an increasing workload.

**Over the study period, the number of Committee meetings has remained constant. The amount of time spent in meetings has increased, still being considered as relevant to the increasing needs.**

Most committees meet on a monthly basis (CAT, CHMP, PDCO, PRAC), the meetings in August are replaced by a written procedure. The COMP meets 11 times per year, whilst the HMPC meets only 6 times per year. The variations in the chart below stem from the fact that some committees were established in the middle of a calendar year.

Whilst the average number of days of meetings per year has remained constant for the CHMP, HMPC and PRAC (with the exception of the year of establishment of the latter), the number of meeting days for the CAT, PDCO and COMP has increased over the past years. CAT and COMP were extended to 3 days (instead of 2), whilst for PDCO the meeting time increased from 3 to 4 days. The majority of experts (81%) considered this to be adequate.

**EMA was able to successfully adapt to a higher than expected workload with its performance remaining high on key tasks.**

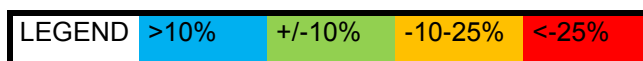
When looking at indicators on the workload<sup>36</sup> over the past four years it is interesting to note that the workload was larger than expected in some years, whilst at the same time this did not have a negative effect on the effective functioning of the system. When looking at pre-authorisation activities, the number of scientific advice requests or ATMP classifications were higher than expected in some years. The same holds for the percentage increase in scientific-advice requests. Yet the number of scientific procedures completed within regulatory timeframes were always around 100%, as shown in the figure below without having an effect on the effectiveness of the system (see section 3.1)

**Table 9: Performance and Workload indicators – Pre-authorisation<sup>37</sup>**

Performance	2014	2015	2016	2017
Scientific procedures completed within regulatory timeframes	99%	100%	99,50%	100%
Percentage increase in scientific-advice requests	17%	-8%	14%	8%

Workload	2014	2015	2016	2017
Scientific advice and protocol assistance requests	551	510	582	630
Designation of orphan-medicine applications	329	258	329	260
Paediatric-procedure applications	485	515	549	630
Requests for classification of ATMPs	28	61	60	46
Innovation Task Force briefing-meeting requests	27	35	41	33



<sup>36</sup> The indicators are taken from the EMA Annual Activity reports of 2014 to 2017. For each indicator, EMA had provided a forecast as well as an actual value. The colour code describes the relation of the actual value with the forecast. Hence, years with a blue value saw a significantly higher result than expected, whilst years with an orange or red value saw a significantly lower result than expected.

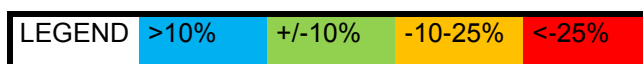
<sup>37</sup> EMA, Annual Activity Reports 2014-2017

The same trend can be observed when looking at pharmacovigilance activities. The number of signals the EMA has peer-reviewed and validated have constantly been more than expected, judging by the indicators from the EMA annual activity report. Yet reporting requirements have not been significantly affected, apart from a small decrease regarding reaction-monitoring reports, as shown in the table below.

**Table 10: Performance and workload indicators – Pharmacovigilance<sup>38</sup>**

Performance	2014	2015	2016	2017
Reaction-monitoring reports supplied to the lead Member State monthly	100%	100%	97%	97%
Protocols and reports for non-interventional post-authorisation safety studies assessed within the legal timeframe	100%	98,40%	100%	100%

Workload	2014	2015	2016	2017
Number of signals peer-reviewed by EMA	2030	2372	2372	2062
Number of signals validated by EMA	34	61	61	82



### 3.3. Does the system rely on adequate capacities and expertise?

3.3.1. The level of involvement of NCAs is considered as adequate overall to support the effective functioning of the system

**The strength of the EMRN is the existence of a European-wide network for marketing authorisations consisting of multinational expertise.**

Through interviews, stakeholders considered that the Network overall has enough resources, internal skills and benefit from the expertise from the Member States. The online survey with experts found that the majority of experts (92%) considered the overall organisation to be clear and effective to achieve the aims of their committees and working parties.

**The level of participation of experts from NCAs has indeed increased over the study period.**

The 2010 study found that the EMA Secretariat and NCAs should encourage more experts at the NCA level to be exposed to European procedures in order to foster harmonisation in evaluation practices and increase the number of knowledgeable experts that could be solicited for any given assessment. Case Study interviews in e.g. Germany, Estonia and Denmark identified an increase in NCA staff participation in EMA-related activities. One small Member State consulted through the case studies indicated that since joining the EU, the assessors within the NCA have had to change their priorities from national level work to EU level procedures in order to address the demands of national pharmaceutical companies, which preferred using European procedures to national ones. In a larger Member State, it was indicated that more than 50% of capacity is spent on European procedures, with a marked increase in the level of participation of staff within the NCA in the last ten years.

**Scientific expertise provided by the network is considered adequate to address scientific needs and allow the committees to issue credible opinions. Expertise is not equally brought by all MS,**

<sup>38</sup> EMA, Annual Activity Reports 2014-2017

**but their participation in committees' meetings and MNAT contribute to the development of expertise of the whole system.**

Whilst 51% of experts responding to the online survey considered that the scientific expertise is adequately distributed throughout the Member States, 35% did not consider this to be the case. In the open responses experts noted that there was still a significant difference in expertise between Member States, with 'older' and larger Member States having a broader expertise available. The goal should thus not be to ensure expertise is equally spread throughout the Network but that every Member State has some kind of expertise that can contribute to network activities on the European level. For instances where this is not the case yet, Multinational Teams provide an opportunity to address this.

Concerning the level of expertise of all members of the Committees and Working Parties, 53% of respondents considered that all members of their Committee/Working Parties have the right level of expertise to contribute to and take decisions. 32% of expert respondents considered, however, that this was not the case. Those who disagreed stated that at times, the expert from the Member State with the relevant expertise is not available within an NCA, leading to the NCA appointing members to certain committees who did not have the optimal expertise for the subject. Others pointed out that members that had the relevant expertise in one area, might not have it in another, e.g. academic experts with limited knowledge of regulatory specificities (e.g. a comprehensive understanding of the specific EU legislation applying to orphan drugs).

However, these occurrences did not hamper the effectiveness of the work in the Committee, as attendants without the right expertise would not affect the opinion issued, but rather be silent observers. This is supported by the fact that 75% of respondents to the online survey considered the nomination of experts to be appropriate to address the needs in relation to scientific expertise, with only 15% identifying room for improvement in this regard. **Essentially, these findings mean that whilst not all members of Committees may have the relevant expertise individually, the Committee as a whole has sufficient expertise to provide a credible opinion.**

Some experts proposed to increase the expertise available in Committees by nominating experts purely based on their relevant credentials rather than based on MS representation, claiming that this would benefit the average level of expertise in Committees. However, it could have a negative effect on the system. Nominating experts purely based on credentials makes it harder for slightly less qualified experts to attend Committees and build their expertise. This would also have a negative effect on smaller Member States, as they would be limited to participating in certain areas.

Thus, as expertise across all Member States is not yet fully developed, it is preferential to maintain the current system. It ensures that the relevant expertise is available, but at the same time allows for the development of credentials and the overall development of expertise in the system.

**Gaps in expertise exist in certain areas of high relevance for tackling future challenges.**

There is a consensus among the several types of stakeholders that expertise needs to be reinforced in some scientific areas. 42% of expert respondents either strongly agreed (5%) or agreed (37%) with the statement that gaps in expertise exist in their Committees/Working Parties in which they were involved. NCAs specified that there was potential to build expertise in the area of ATMPs and the intersection of medicines and medical devices, where the lines are becoming increasingly blurred, and that this requires additional expertise, which is not necessarily present at the moment. This was confirmed by representatives interviewed from pharmaceutical industries who identified some knowledge gaps in relation to some of the more 'sophisticated' medicinal products. EMA shared the same point of view and stated that the gap in this area can present a challenge for innovators in Europe.

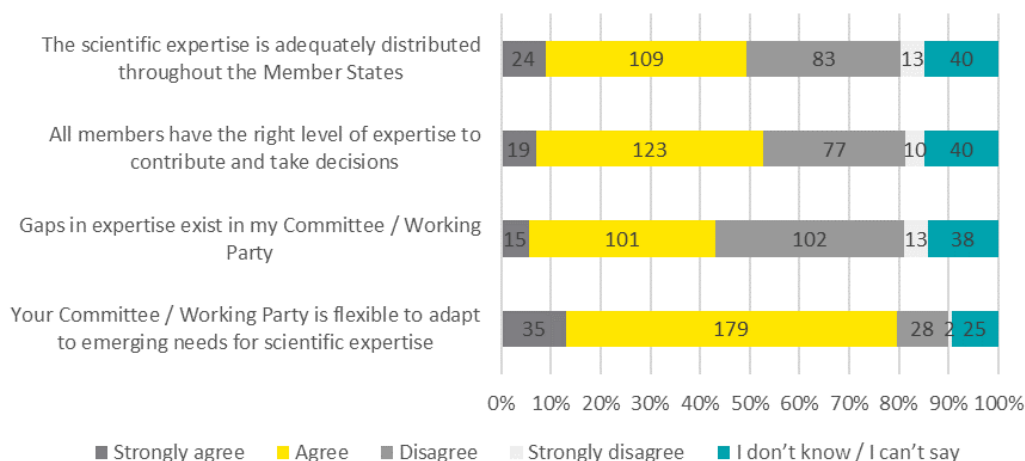
Another area in which stakeholders from the EMA Secretariat, the Commission and NCAs identified gaps in expertise was in relation to **the treatment of big data and the use of artificial intelligence**. These areas are seen as an expertise gap which would need to be addressed in the coming years in order to ensure that the work of the network remains current and up to date. Stakeholders identified the need for capacity-building on statistical methodologies which support adaptive clinical trials, clinical trial design expertise and digital health.

**The network is perceived as flexible enough to adapt to evolving challenges.**

A certain level of flexibility existed within the Committees and Working Parties. 80% of expert respondents either strongly agreed (14%) or agreed (66%) that their Committee/Working Party was flexible to adapt to emerging needs for scientific expertise.

This flexibility was acknowledged, overall, through interviews with NCAs through case studies who considered that whilst expertise gaps could exist in some instances, the structure was considered to be sufficiently flexible to be able to adapt to existing and future gaps.

**Figure 14: With regard to the expertise in place, to what extent do you agree with the following statements?**



Source: Expert Survey

### 3.3.2. The collaboration and experience of Member States has increased over the 10-year period with this also seen in rapporteurships and multinational teams

**Overall, the collaboration and experience of Member States has increased over the study period, benefitting both CP and MRP/DCP.**

Whilst there were challenges faced by the network in the last study period to ensure the integration of acceding Member States to the regulatory network, the network has focused in this ten-year period on increasing collaboration and expertise of smaller and newer Member States in the overall process.

National competent authorities consulted during interviews and case studies considered that overall collaboration between Member States was increasing and was considered to be of added value. The collaboration notably facilitated interaction between NCAs when dealing with MRP and DCP.

The shifting trends are visible when looking at the appointment of rapporteurships during the study period.

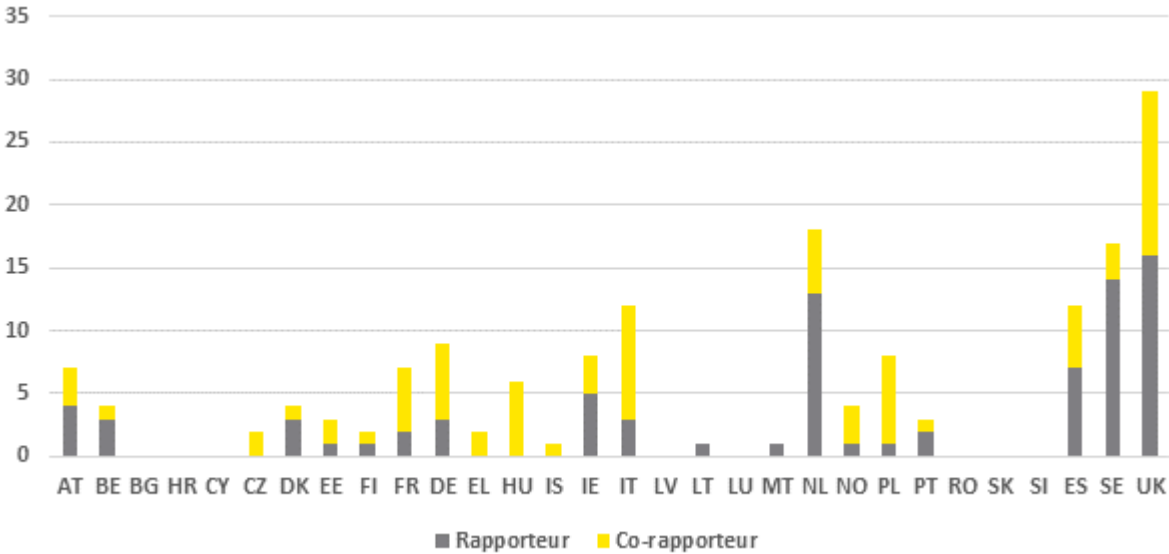
#### Box 5: Rapporteurship

The rapporteur is a committee member who together with the co-rapporteur (in the majority of case) leads the evaluation of an application. This includes preparing the assessment reports as well as leading the discussions in the committees. An NCA that provides the rapporteur for one application is responsible for accompanying the product throughout its lifetime (also post-authorisation).

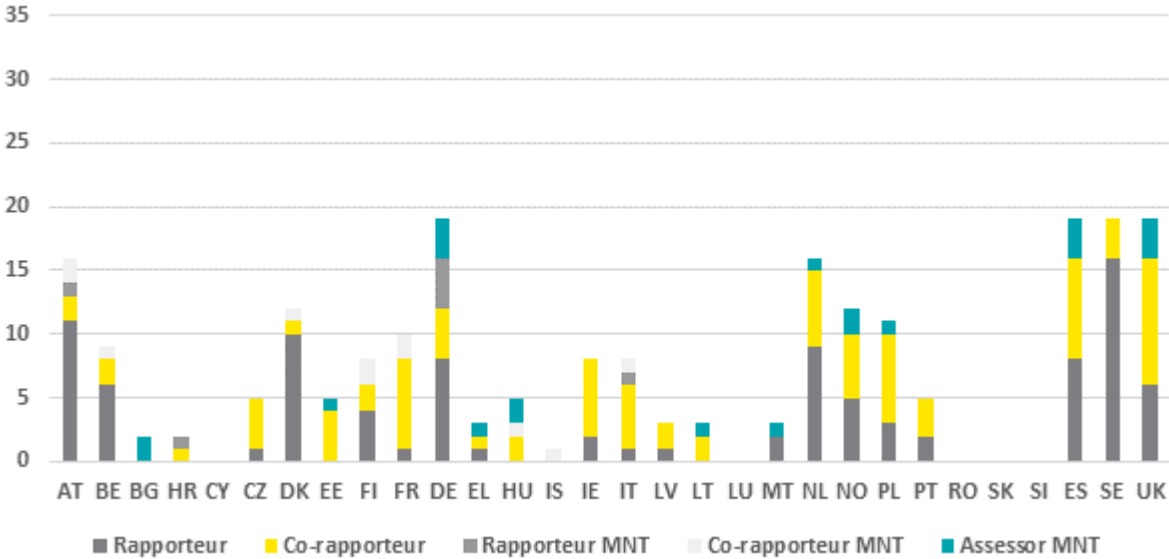
**Rapporteurship is still dominated by a few, prominent Member States.**

When looking at the evolution of CHMP rapporteurship and co-rapporteurship between 2013 and 2017, it is apparent that some Member States, such as the United Kingdom, the Netherlands or Sweden, continue to lead a large amount of procedures. At the same time, their total number of projects in which they are involved has declined, with a number of smaller Member States increasing their involvement over the reference period. Nonetheless, there are still some Member States, such as Romania, Slovak Republic and Luxembourg, who remain uninvolved in rapporteurship activities.

**Figure 15: CHMP Rapporteurship 2013<sup>39</sup>**



**Figure 16: CHMP Rapporteurship 2017<sup>40</sup>**

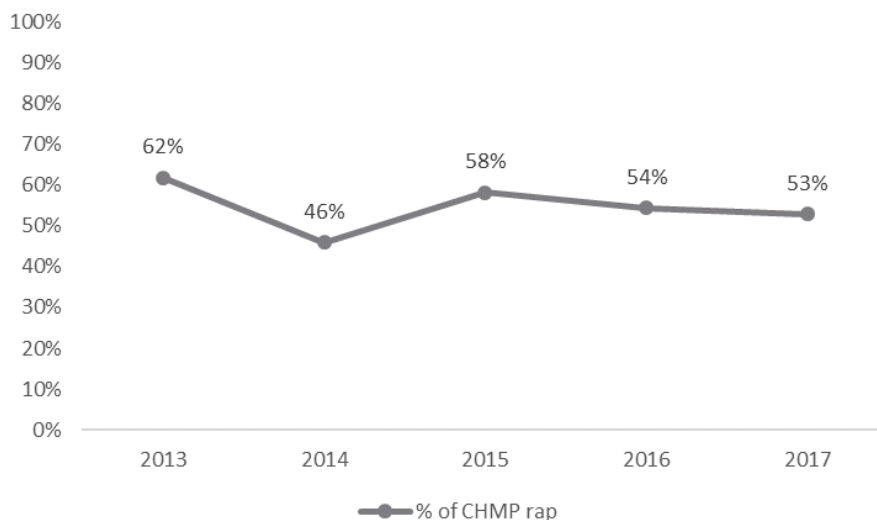


In the CHMP, five Member States (Austria, Germany, Netherlands, Sweden and the United Kingdom) have regularly accounted for more than 50% of all rapporteurships.

<sup>39</sup> EMA, Annual Report 2013

<sup>40</sup> EMA, Annual Report 2017

**Figure 17: Percentage of CHMP Rapporteurship held by most present Member States<sup>41</sup>**



**Multinational teams have helped counteract the clustering of expertise in a few Member States.**

The concept of Multinational Teams (MNAT) was introduced in 2015 for the Centralised Procedure, where a rapporteur can lead a team of experts from different NCAs. Two MNATs were set up in 2015, with 10 in 2016 and nine in 2017. Germany leads the most MNATs with three in 2016 and four in 2017. Interviews found the benefit of the creation of MNATs in order to provide Member States with the opportunity to participate in dossiers.

The use of Multinational Teams was identified by stakeholders within the EMA Secretariat, the Commission and NCAs as providing added value and ensuring that smaller Member States can play a role. Interviews during Member State Case Studies identified the added value such teams brought to smaller Member States in increasing their level of expertise on specific issues. NCAs also noted that Multinational Assessment Teams had helped building collaboration between agencies.

**A clustering of procedures by MS can also be observed for the MRP/DCP.**

Throughout the study period, a large part of MRP & DCP procedures were finalised by five RMS, namely the Netherlands, Germany, the United Kingdom, Denmark and Portugal. Together, these Member States accounted for around 70-80% of finalised procedures. As such, the high number of finalised procedures by a few MS could be explained to an extent by the targeting of the respective markets by the industry. Nonetheless, as there is an equal distribution of CMS across Member States, there exists the potential to further distribute RMS, as most products do not seem to be markets specific.

**Multiple applications for the same medicinal product under the DCP do not seem to be an issue.**

NCAs reported that coordination on this issue worked well, with Germany, Denmark and Spain pointing out that whilst there are no formalised mechanisms to tackle this, exchanges between NCAs work well and any duplicated are spotted early in the process. They furthermore stressed that the ultimate responsibility lies with the applicant, and that measures are taken by the NCAs to inform and if necessary sanction the applicant once a parallel application become apparent.

### 3.4. To what extent is the current architecture of the regulatory network and its functioning efficient? Are resources sufficient and allocated in a way

<sup>41</sup> EMA, Annual Reports 2013-2017



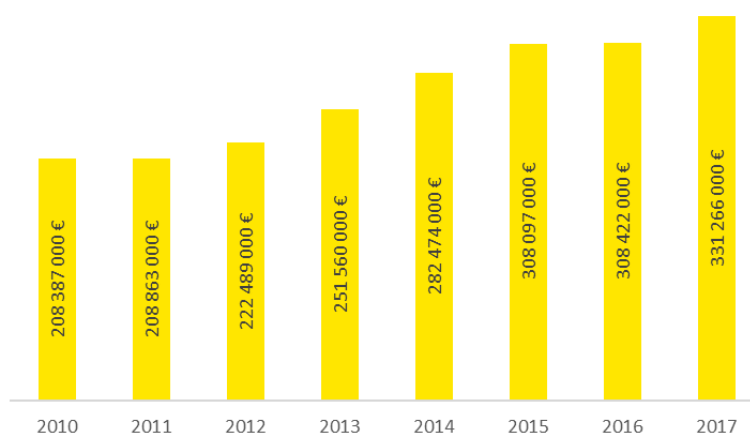
## that is proportionate to the results and outputs delivered?

3.4.1. The budget of EMA has increased over the study period, pushed by a growing fee-financed workload and new tasks

### The budget of EMA has constantly grown over the last years.

It increased from EUR 208,4 million in 2010 to EUR 331,3 million in 2017. This reflects a total increase of around 60% and an average annual growth of around 6,3%.

Figure 18: EMA budget<sup>42</sup>



### Box 6: EMA accounting principles

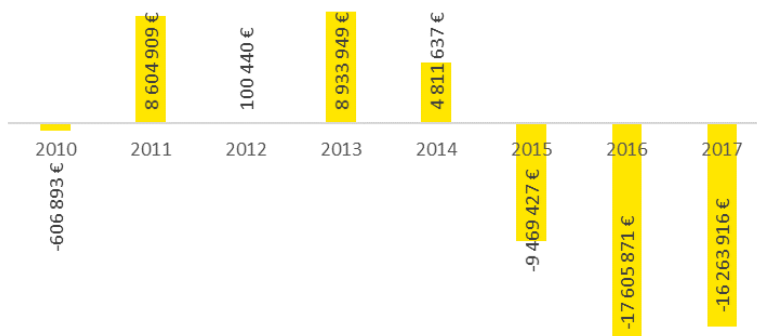
To fully understand the budgetary details of EMA, it is important to note the accounting principles of EMA. Firstly, EMA as an agency of the European Union cannot make a profit or a loss. Hence, the budget presented above reflects both the planned revenue as well as the planned expenditure. At the end of a financial year, EMA uses two distinct accounting techniques, accrual accounting and budget accounting. Accrual based accounts (standard accounting principles) are cash-based and record all events and operations which affect the economic and financial situation and the assets and liabilities of EMA in a chronological order using the double entry method. The budgetary accounts (Agency specific accounting principles) on the other hand, provide a detailed record of the implementation of the budget, and differ by using elements such as carry-overs.

### Budgetary results vary significantly between accrual-based accounting and budgetary accounting.

Looking at accrual-based accounts, the year-end economic result turned negative in recent years, resulting in a negative outturn. This is however likely due to the move to a new building and the preparation and implementation of the move of the Agency to Amsterdam, which would require resources to be mobilised in the short term.

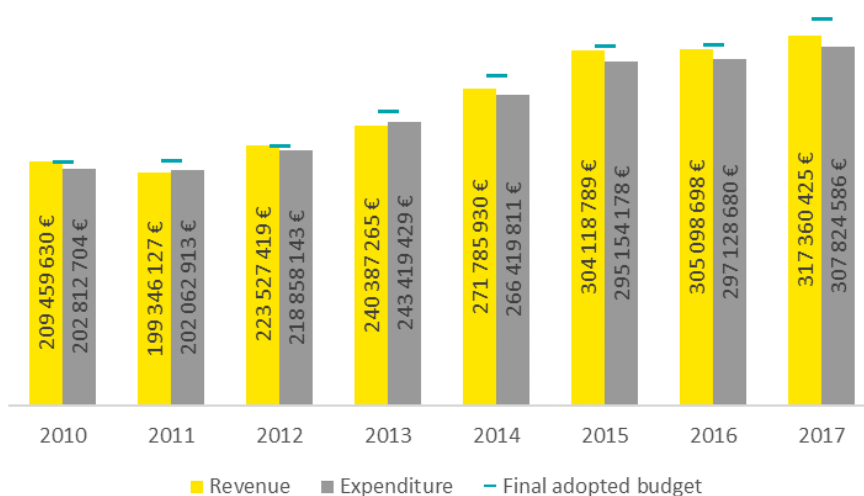
<sup>42</sup> EMA Final annual accounts 2008-2017

**Figure 19: Economic Result (accrual basis)<sup>43</sup>**



Whilst accrual-based accounts can include negative or positive economic results, budgetary accounts ensure a balanced budget at the end of every year. Positive deviations from the foreseen budget are balanced by reimbursements to the Commission, and negative deviations are carried over to the next year. Over the study period, according to budgetary accounting, expenditures only exceeded revenue twice (2011, 2013), and after taking into account appropriations from the previous year and differences in exchange, led to a negative outturn for the year only once (2011). Furthermore, expenditures were always within the budget, pointing to an overall efficiency of the system.

**Figure 20: Budget, expenditures and revenue (budgetary accounting)<sup>44</sup>**



**The rise in revenue of the study period is mainly based on an around 75% increase in revenue from fees.**

According to EMA budgetary contributions from the European Commission have stayed relatively stable. Whilst the number of initial marketing authorisation applications has stayed constant over the years, the rise in fees comes from the fact that the overall pool of medicines on the market has increased. As a large part of fees come from post-authorisation activities, more medicines on the market mean a higher revenue. However, as fees are outside of the scope of this study, the issue will not be investigated further. This includes the transfer and repartition of fees between EMA and the NCAs.

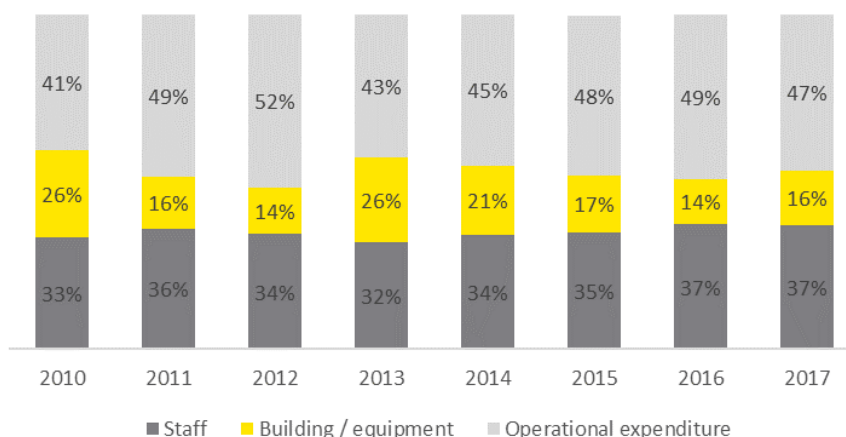
<sup>43</sup> EMA, Budget 2010-2018

<sup>44</sup> EMA, Budget 2010-2018

**The rise of total expenditure over the study period was driven by staff and operating expenditure.**

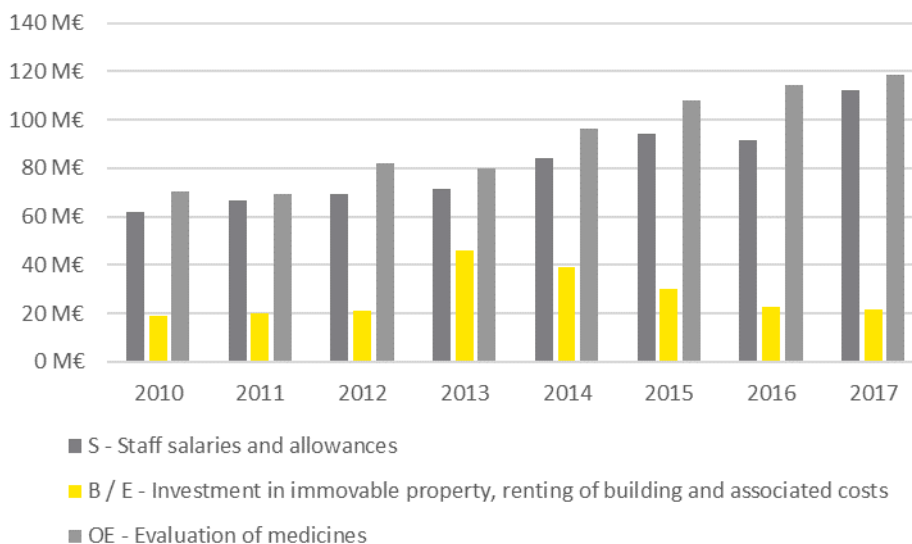
When looking at the three main points of expenditure, namely staff, operating expenditure and building/equipment, the total share of the former two has increased from 74% in 2010 to 84% in 2017. In fact, when looking at the actual values, building/equipment expenditure has remained relatively constant, apart from a minor fluctuation in 2013-2014, at around EUR 50,000,000 per year.

**Figure 21: Total expenditure and repartition<sup>45</sup>**



The rise in overall staff expenditure was driven by the expenditure point of staff salaries and allowances. This point increased from EUR 51,988,000 in 2009 to EUR 112,104,000 in 2017. For operational expenditure, the main driver was the expenditure point on evaluation of medicines (i.e. payments to NCAs), which rose from EUR 66,487,000 in 2009 to EUR 118,692,000 in 2017.

**Figure 22: Main expenditure point by category<sup>46</sup>**



**Staff has increased slightly over the study period.**

The number of EMA employees (not including contract agents and national experts) has reached 596, which is up from 567 in 2010. When including the contract staff and seconded national experts, the total

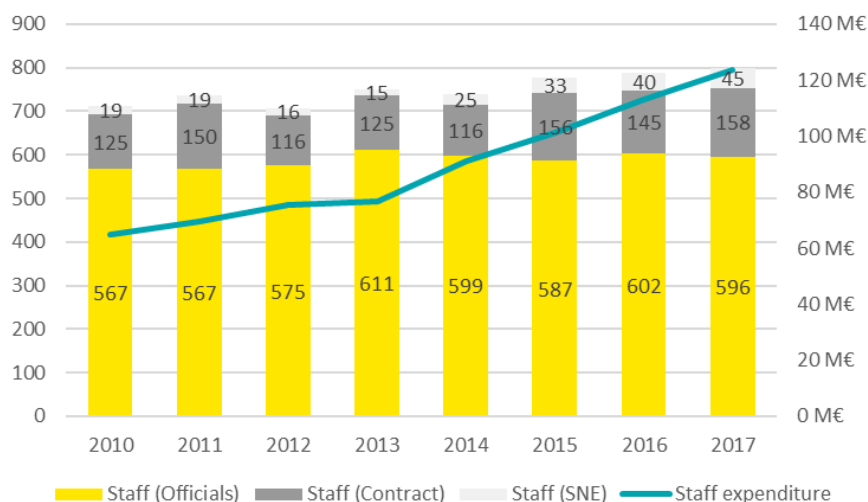
<sup>45</sup> EMA Work Programmes 2011-2017, numbers for 2017 preliminary

<sup>46</sup> EMA Work Programmes 2011-2017, numbers for 2017 preliminary

number of FTE changed from 711 in 2010 to 799 in 2017. The total amount of staff expenditure has increased from EUR 64,7 million in 2010 to EUR 123,8 million in 2017. The fact that staff expenditure has risen more rapidly than the number of staff can be explained by three factors:

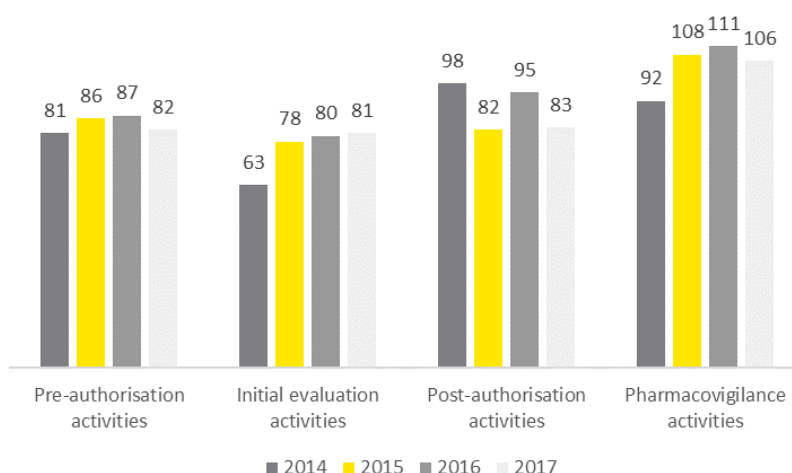
- ▶ Staff gaining seniority and subsequent salary increases according to EU staff regulations;
- ▶ The fact that from 2016 onwards, EMA has to pay employer pension contributions, which were previously borne by the general EU budget;
- ▶ Exchange rate fluctuations between the Euro and the British Pound, which were significant especially in recent years.

**Figure 23: EMA staff and staff expenditure<sup>47</sup>**



When looking at the development of staff by activity over the past years, this idea is partly supported. A clear increase in staff can be seen in the field of pharmacovigilance activities, aligned with an increased focus of EMA on this area, as exemplified by the previously mentioned creation of PRAC. However, the increase in staff in the area of initial evaluation activities is unaligned with the relatively constant level of applications received (further elaborated in WP3).

**Figure 24: Evolution of staff by area of activity<sup>48</sup>**



<sup>47</sup> EMA, Budget 2010-2018 & Annual Accounts 2010-2017

<sup>48</sup> EMA, Annual Activity Reports 2014-2017

### 3.4.2. The frequency of meetings of EMA, though high, responds to existing needs and is necessary

**Whilst the frequency of meetings is considered as necessary, issues can arise in relation to the overall timing of different meetings.**

Interviews with stakeholders at national and EU level highlighted that issues related to the timing of the meeting can exist when several committees need to provide opinions. A particular example was provided in relation to the time that can run between when a meeting of the CHMP and COMP is held and when an opinion is provided on an orphan drug. This points to the potential for the Secretariat to play a more prominent role in communicating the conclusions from other committees. Moreover, the timing of meetings at times does not permit members of two different committees to be in attendance with conflicts in the schedule.

Concerning meeting agendas, 77% either strongly agreed (16%) or agreed (61%) that the structural agenda of the meetings enabled discussion between members with adequate time for discussion per agenda item. 20% of respondents, however, disagreed that the agenda items enabled discussion during committees. Many of these respondents pointed out that meetings were too long. Whilst some suggested adding an additional day of meetings, others suggested increasing efficiency by ensuring that relevant documentation is available well in advance. Interviews with NCAs highlighted that whilst the timing and agenda of the meetings were not ideal, they were in fact necessary in order to ensure that all items were treated, with NCA experts acknowledging the length and time of the meetings to be burdensome but necessary.

Interviews with the EMA Secretariat also acknowledged the heavy agenda of meetings with it indicating that the more there is a need for specific expertise, the more the content of the meeting expands. In order to respond to the heavy agenda, stakeholders from Member States and the EMA Secretariat identified the need for greater IT and Communication tools, as further discussed under Work Package 5 below.

### 3.4.3. Resources allocated to Network activities have increased within some NCAs.

**The resources allocated by NCAs to Network activities evolved due to different reasons.**

- ▶ **Newer Member States** have increased resources allocated to network activities due to the increase in their involvement. The Estonian NCA reported having to reallocate staff from national procedures to the EU-level, as since joining the system in 2006 the work deriving from EU procedures has increased significantly whilst national procedures have decreased. A similar situation can be found in the Czech Republic, which has invested heavily in training more experts. This was done as a response to a period between 2007 and 2008, where the NCA did not have enough qualified individuals to participate in assessment tasks.
- ▶ NCAs of **larger Member States** identified the need to allocate more resources to EU-level procedures due to the growing complexity. The German NCAs note for example that reporting and committee participation requirements on CP procedures had increased, requiring the NCA to allocate more resources. The Spanish NCA raised a similar point, noting that across the Network, resources allocated to the CP seem to increase, leaving less for national procedures.
- ▶ **Medium-sized Member States** have differing experiences. In Denmark, NCA staff allocated to EMA activities has increased from 10% to 12% over the past years and is expected to further increase over the next years due to the rising complexity of EMA's work. Sweden, however, has been able to maintain a stable level of overall staff and staff allocated to EMA activities. This could be due to the fact that they have had a strategy to be highly involved in EU-level procedures from the start of their membership in 1996.

## 4. Work Package 2: Procedures Preceding Submission of Marketing Authorisation Applications

The aim of this Work Package is to examine the extent to which procedures preceding submission of Marketing Authorisation applications effectively and efficiently support the achievement of the network's regulatory objectives, especially in terms of facilitating access to marketing authorisations, fostering innovation and competitiveness and ensuring patients' access to reliable medicines.<sup>49</sup>

In detail, this section aims to answer four questions:

1. Do pre-submission activities answer the needs of the stakeholders and facilitate access to marketing authorisation procedures?
2. Do pre-submission activities support the achievement of the objectives of the EU regulatory framework for medicinal products in terms of innovation and competitiveness?
3. Do pre-submission activities support the achievement of the objectives of the EU regulatory framework for medicinal products in terms of quality of subsequent scientific outputs and safety for patients?
4. Are pre-submission activities efficient in terms of costs incurred from both the industry and the EMA network to achieve the expected output?

### Synthesis

Pre-submission activities have increased over the study period:

- ▶ Requests for scientific advice have increased from 332 to 471
- ▶ Support to SMEs has also increased, with the total number of SMEs registered rising from 1258 to 1893
- ▶ ATMP classifications have increased from 20 to 46
- ▶ Orphan designations submitted have increased from 174 to 260
- ▶ PIP procedures have increased from 318 to 421

In light of pharmaceutical companies requesting scientific advice more often over the past years, the **resource allocation at a secretariat level seems efficient**. This is furthermore underlined by the fact that EMA has managed to strengthen and implement **procedures to foster competitiveness and accompany the development of innovative products** from an early stage.

- ▶ Mechanisms such as the Innovation Task Force allow stakeholders to experience early opportunities for dialogue, encouraging the development of innovative products.
- ▶ PRIME is a step forward of EMA, to catch up with similar procedures already implemented by e.g. the FDA.
- ▶ The adaptive pathways pilot showed good initiative, but its implementation was not optimal both

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<sup>49</sup> Regarding terminology, this chapter distinguishes between pre-submission activities and pre-authorisation activities. Pre-authorisation activities refer to activities undertaken specifically by EMA, whilst pre-submission activities refer to all relevant activities of the network (in line with the ToR of this study)

related to the success rate and the communication efforts. This led to a general scepticism among patient organisations, which can pose a barrier to the effective implementation of a successful pilot.

In general, all types of stakeholders consulted agreed that the approaches put in place support innovation and competitiveness have had an impact. EMA is proactive in trying to develop along with the needs of the market to ensure competitiveness and innovation.

Scientific guidelines provide a good documentary basis for pre-submission advice. Nonetheless, their clarity could be improved, and they could be reviewed and updated more frequently, especially regarding innovative areas.

At the EU-level, the SAWP presents an effective mechanism for providing scientific advice. At the same time, dedicated committees fulfil their role successfully.

- ▶ CAT provides an opportunity to discuss ATMPs, although its visibility could be increased
- ▶ PDCO plays an important role in paediatric medicines, but its role with respect to the CHMP needs to be strengthened and the PIP procedure simplified
- ▶ Orphan designations by COMP could be better aligned with CHMP decisions

At the same time, many NCAs have put in place their own pre-submission assistance mechanisms such as national innovation offices.

There are some potential **efficiency gains** regarding cooperation and coordination. Notably, these concern Committee coordination, repartition of early stage advice between EMA and NCAs, as well as the cooperation between HTA bodies and EMA/NCAs, to ensure products which go through the EMA procedures will eventually reach the market.

Legislative exceptions such as compassionate use allow the system to show flexibility in specific cases.

International cooperation increased harmonisation through joint GMP inspections and bilateral agreements. Thus, through both European and international efforts, there exists a solid basis to ensure both the quality of scientific outputs and the safety of patients.

Whilst the system is functioning well, it is important to ensure that its achievements are not tainted by a perception of bias, which could arise through cooperating too closely with the pharmaceutical industry on pre-submission advice. The inquiry of the Ombudsman confirms that **clear and formalised procedures are necessary to ensure the trust in the system persists**.

## 4.1. Do pre-submission activities answer the needs of the stakeholders and facilitate access to marketing authorisation procedures?

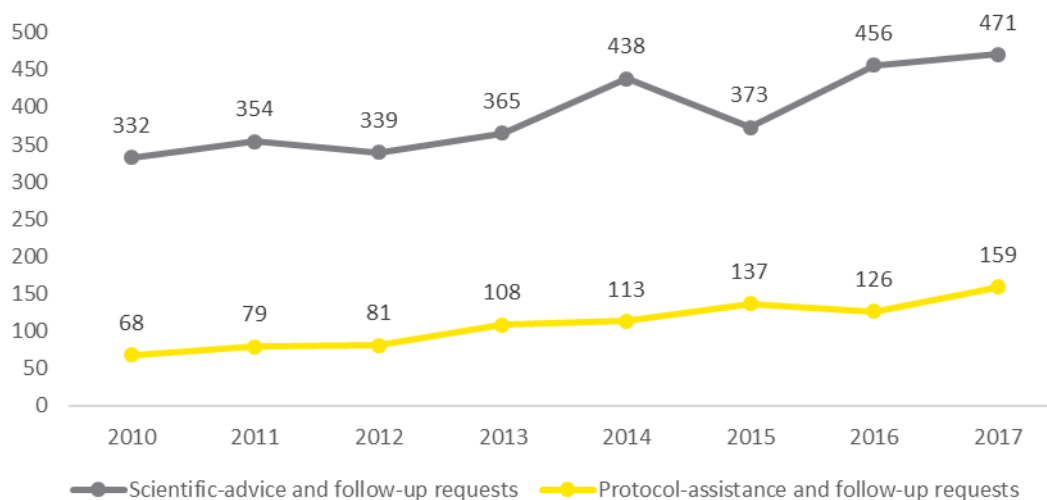
### 4.1.1. EMA Scientific Advice supports the effectiveness of the system

**The number of scientific-advice and protocol-assistance requests have significantly increased over the past 10-year period.**

Whilst EMA received 332 scientific-advice and follow-up requests in 2010, the number increased by around 50% by 2017 in reaching 471. The number of protocol-assistance and follow-up requests rose from 68 in 2010 to 159 in 2017, which shows an even greater increase.



**Figure 25: Scientific-advice and protocol-assistance requests received<sup>50</sup>**



**The positive contribution of scientific advice was underlined by industry stakeholders.**

The feedback provided through regulatory and scientific advice on certain doubts during development and submission is appreciated and valued, with EMA scientific advice perceived by this group of stakeholders as clear and predictable in view of timeliness and procedures. However, most pharmaceutical industry representatives interviewed stressed that EMA's scientific advice is costly, quite formal and focused on reaching consensus among regulators instead of allowing for an open discussion.

In the area of scientific advice, the EU system has a distinct advantage over the United States' (US) system from a regulatory view. Whilst scientific advice in the EU presents a recommendation and guidance, it is binding in the US. This can lead to instances where the hands of regulators are tied when new scientific developments arise, as pharmaceutical industries can base their application on precedent scientific advice. Whilst industry stakeholders in Europe have also called for scientific advice to be binding to provide them with more security, this would put restraints on the reactivity of the regulatory system and thus ultimately have an impact on patient safety.

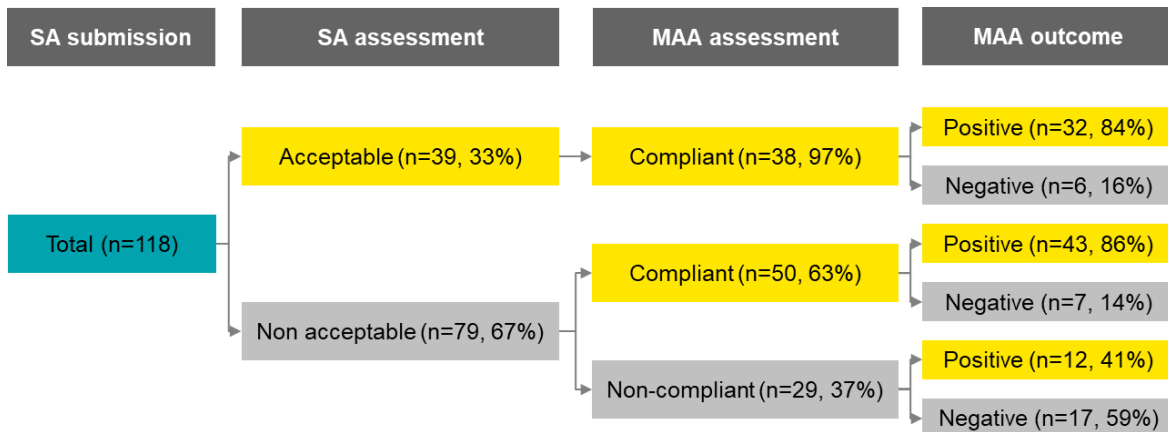
Scientific literature confirms a positive impact of scientific advice on the marketing authorisation application (MAA) outcome. In an article published in *Nature Reviews*, Hofer et al (2015)<sup>51</sup> have found that products going through scientific advice have a higher chance of a positive MAA outcome. The study investigated the effect of scientific advice on medicines authorised through the centralised procedure between 2008 and 2012.<sup>52</sup> It found that whilst more than 80% of applications who received SA and complied with the recommendations received a positive MAA outcome, the value was 41% for those who received SA but did not comply. At the same time the study shows the effectiveness of the authorisation procedures in ensuring an impartial and thorough screening, as receiving SA and complying with it does not guarantee a positive outcome.

<sup>50</sup> EMA, Annual Reports 2009-2017

<sup>51</sup> Hofer, M. P., Jakobsson, C., Zafiroopoulos, N., Vamvakas, S., Vetter, T., Regnstrom, J., & Hemmings, R. J. (2015). Regulatory watch: impact of scientific advice from the European Medicines Agency. *Nature Reviews Drug Discovery* 14, 302–303

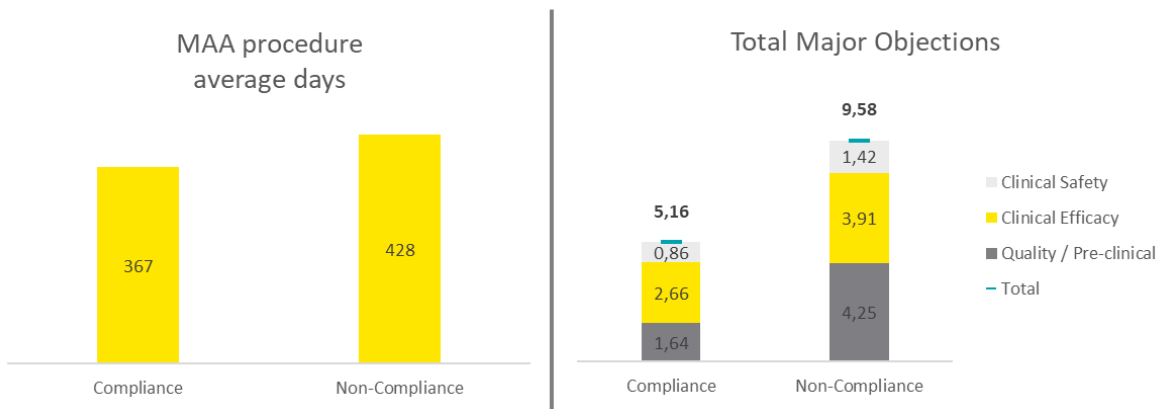
<sup>52</sup> Note that whilst part of the timeframe falls out of the scope of this report, due to a lack of disaggregated data, the full findings are presented.

**Figure 26: Outcome of MAA after SA<sup>53</sup>**



In addition to the positive effect on the outcome of the MAA, applications that benefitted from SA went through the subsequent MAA procedure more quickly than those who did not. In fact, the average difference amounted to 61 days, meaning products benefitting from SA completed the procedure around 2 months faster. They also received significantly fewer major objections at CHMP assessment days 120 and 180.

**Figure 27: SA compliance effects on procedural aspects<sup>54</sup>**



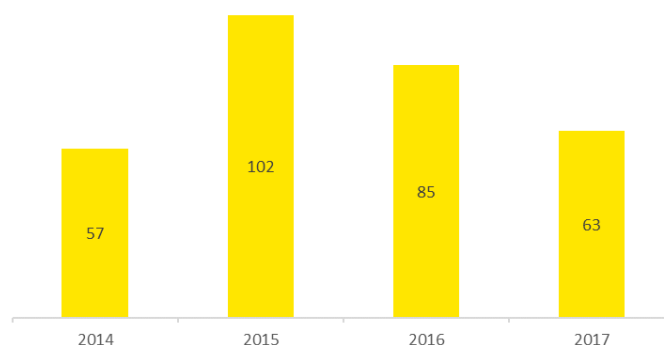
**Pre-submission meetings are well received by all stakeholders.**

The meetings, which take place 6 to 7 months before MAA and include the procedure manager and the EMA product lead, were noted by industry stakeholders to have high added value, especially for more difficult and complex applications. The large majority of experts involved in CP pre-submission meetings also noted their benefit, especially to ensure the optimal preparation of the procedure, discuss the way forward and streamline communication. They also help lower the risk of missing information when the evaluation starts.

<sup>53</sup> Hofer, M. P., Jakobsson, C., Zafiroopoulos, N., Vamvakas, S., Vetter, T., Regnstrom, J., & Hemmings, R. J. (2015). Regulatory watch: impact of scientific advice from the European Medicines Agency. *Nature Reviews Drug Discovery* 14, 302–303

<sup>54</sup> *ibid.*

**Figure 28: Pre-submission Meetings<sup>55</sup>**



### **Product Case Study 2: FAMPYRA**

An application for marketing authorisation was made for the product Fampyra, a product designed for adult patients who have multiple sclerosis with walking disabilities.

Following agreement on the eligibility to apply to the centralised procedure in May 2009, the CHMP issued a negative opinion in January 2011. Further to the re-examination of the dossier, the CHMP issued a positive opinion in May 2011, with a conditional marketing authorisation granted in July 2011 and subsequently transferred to a full marketing authorisation in May 2017.

Through the examination of this product's life cycle, the applicant did not seek scientific advice at the CHMP at the pre-submission stage. During the assessment procedure, the CHMP issued a negative opinion with a positive opinion only granted following the provision of additional data. The duration of this overall procedure can indicate the added value of requesting pre-authorisation advice from the EMA in order to ensure the overall quality of the application and thus the quality of the product moving forward.

#### **4.1.2. Committees and Working Parties dedicated to pre-authorisation activities fulfil their role though certain challenges exist**

There is one Working Party and three committees that play an important role specifically in pre-authorisation activities on a central level, the Scientific Advice Working Party, the Committee for Advanced Therapies (CAT), the Committee for Orphan Medicinal Products (COMP) and the Paediatric Committee (PDCO). The role of each Committee/Working Party in pre-authorisation activities is clearly defined by the legislation and the respective RoPs. Overall, the committees effectively fulfil their roles, nonetheless each faces a few challenges that need to be addressed.

**The Scientific Advice Working Party (SAWP) provides a mechanism dedicated to rendering scientific advice and protocol assistance and its work is considered to be effective.**

The SAWP has 36 members, including three members each from the other three mentioned committees, COMP, CAT and PDCO. Its mandate is to provide scientific advice and protocol assistance, it coordinates the input and brings it forth to the CHMP. Its mandate, objectives and rules of procedures are outlined in a specific document.

97% of respondents to the online survey considered the role of this entity to be clear, with the same percentage considering the activities of the SAWP to be appropriate and providing added value. All experts consider that the SAWP provides valuable advice to Marketing Authorisation Applicants, that if taken into account, **makes the application process significantly smoother**. Communication between the SAWP and other committees has improved over the study period, in particular, the increased exchange between COMP and SAWP as well as PDCO and SAWP was noted. These efforts were

<sup>55</sup> EMA, Annual Activity Reports 2013-2017

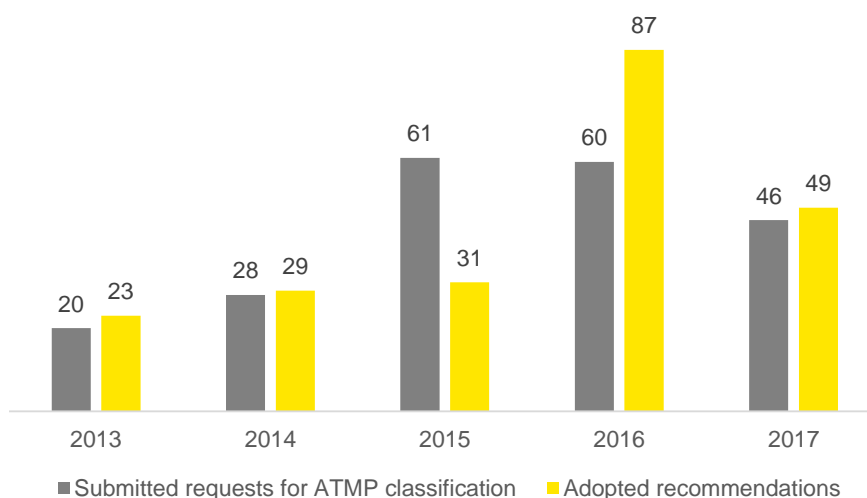
facilitated by the EMA Secretariat and welcomed by all types of stakeholders. There are nonetheless still instances where there exists some misalignment, as previously mentioned (see 3.1.1).

**The CAT has two important tasks, classification and certification of ATMPs.**

**Classification** is a simple, 60-day procedure that does not have a fee. The CAT investigates the product in the early development stage to determine whether it is an ATMP or not. This helps the applicant have regulatory certainty on the status of the product and helps determine which guidelines should be consulted. Once a product is classified as an ATMP based on Article 16(2), applicants requesting scientific advice are entitled to either a 65% fee decrease or to a 90% fee decrease. The 90% fee decrease applies only if the applicant falls under the SME category.

The number of adopted ATMP classification recommendations rose from 23 in 2013 to 49 in 2017.

**Figure 29: Number of recommendations on ATMP classification<sup>56</sup>**



Concerning the classification of ATMPs, the majority of respondents from CAT and the CHMP to the online survey considered the classification of ATMPs to be adequate in terms of its scope and its outcome, with 24% disagreeing with this adequacy. This finding is supported by responses to the written questionnaire by NCAs where 17 out of 22 NCAs agreed or strongly agreed that the classification of ATMPs was effective. However, experts noted that classification of products remains a national competence, thus the CAT outcomes are purely recommendations and not legally binding. Around 10 experts stated that these outcomes should be made binding in order to provide the applicant with certainty. However, around 5 others noted that it was important to keep them as a recommendation, as they are based on early data and results can change in the process. Two NCAs agreed with the proposal to make recommendations binding, whilst one stated that even though not binding, the recommendations already set an EU standard.

When considering the extent to which the classification of ATMPs could be further extended, 45% of respondents from CAT and the CHMP considered that the concept of classification could be extended with 16% considering that such extension should not occur. The significant part of respondents (39%) felt they could not say whether this should occur. Around 10 experts and 2 NCAs also noted that it would be important to further clarify whether products are actually medicinal products in the traditional sense, as they enter into a borderline area such as tissues, cells or medical devices.

<sup>56</sup> EMA, Annual Reports 2013-2017: the annual number of adopted recommendations may be higher than the application submitted because some procedures were started in previous years

### Product Case Study 3: STRIMVELIS

During the authorisation procedure of STRIMVELIS, an ATMP product designated as an orphan medicine, CAT was involved in consulting the national Notified Bodies on the Environmental Risk Assessment of the GMO as the ATMP is a gene therapy product. The Rapporteur's first Assessment Report was circulated to all CAT and CHMP members, and CAT and CHMP agreed on the consolidated List of Questions to be sent to the applicant. Later in the process, CAT and CHMP agreed on a List of Outstanding Issues to be addressed by the applicant.

The procedure showed a successful example of CHMP and CAT cooperation. CAT drafted conclusions and recommendations on which the CHMP relied on to grant its opinion. CAT's involvement allowed to provide the required expertise on Advanced ATMPs.

The second important area of activity of the CAT is **certification**, which is aimed directly at SMEs. In addition to the financial incentive in the form of a fee decrease, SMEs developing ATMPs may also benefit from the certification procedure conducted by the CAT. Article 18 of the Regulation (EC) No 1394/2007 provides that "*SMEs developing an advanced therapy medicinal product may submit to the Agency all relevant quality and, where available, non-clinical data required (...), for scientific evaluation and certification*".

The certification procedure, although independent from the marketing authorisation assessment, aims to facilitate SMEs to develop ATMPs by enabling SMEs to check if quality and/or preclinical data meet the EU requirements for marketing authorisation.

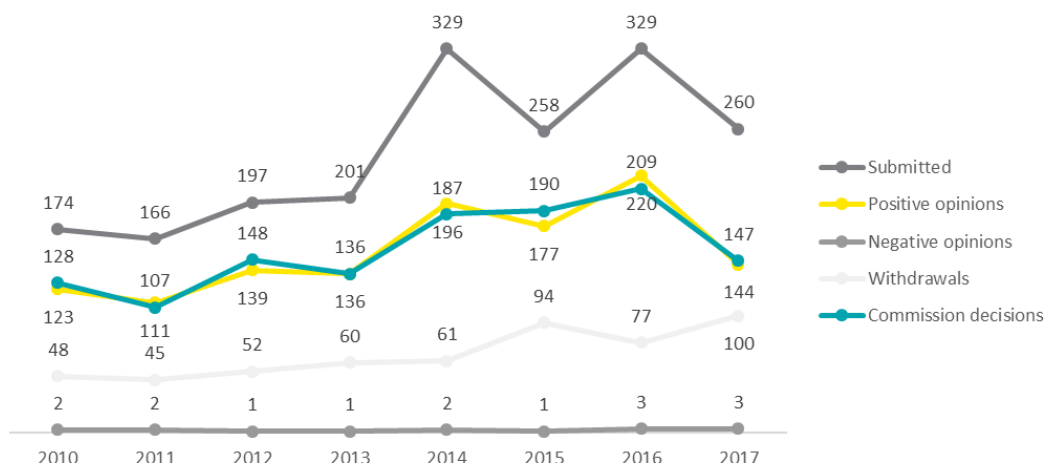
The scope for the procedure concerns studies relying on quality data only or on quality and clinical data. As a consequence, to be eligible for such a procedure, it is preferable that the product has reached a stage of development allowing for sufficient level of available data. This procedure however is not used very frequently, as since 2009, only 12 applications for certifications were submitted, of which 11 were adopted. This reflects an overall very low uptake of certifications.

**Whilst the coordination between COMP and European Commission works well, there are some challenges regarding the interaction with the CHMP.**

The main role of COMP is to evaluate applications for orphan designation, which is given to medicines that are developed to diagnose, prevent and treat rare diseases. Applicants can submit their product for orphan designation to the COMP, which in turn can issue a positive opinion. Subsequently, it requires a Commission Decision to grant the orphan designation.

The number of orphan designations has increased over the past years, with 2015 and 2017 presenting exceptions. Negative opinions remain an exception, it is more likely for a product to be withdrawn. Generally, positive opinions result in a Commission decision.

**Figure 30: Orphan medicinal product designation procedures<sup>57</sup>**



**The designation process requires cooperation between COMP and the Commission.**

The involved parties note that this process is working well with 100% of the experts involved in COMP responding to the survey stating that the interaction allows the Commission to fully take into account the specificities related to orphan medicinal products. At the same time 86% of these experts agree that the procedures in place allow for **smooth interactions between the two parties**. The Commission noted an increase in applications over the past years; however, the overall process still worked well.

The Commission noted that the designation process can at times present a challenge, as **a significant benefit needs to be proven**. This can lead to some instances where the Commission rejects an orphan designation due to evidence not being strong enough.

One challenge for COMP is linked to the mentioned coordination issues with the CHMP on the parallel evaluation of indications, which is described in 3.1.1.

It should be noted there is a parallel study specifically focussed on this area ongoing, and thus an in-depth investigation of orphan legislation was out of the scope of this report.

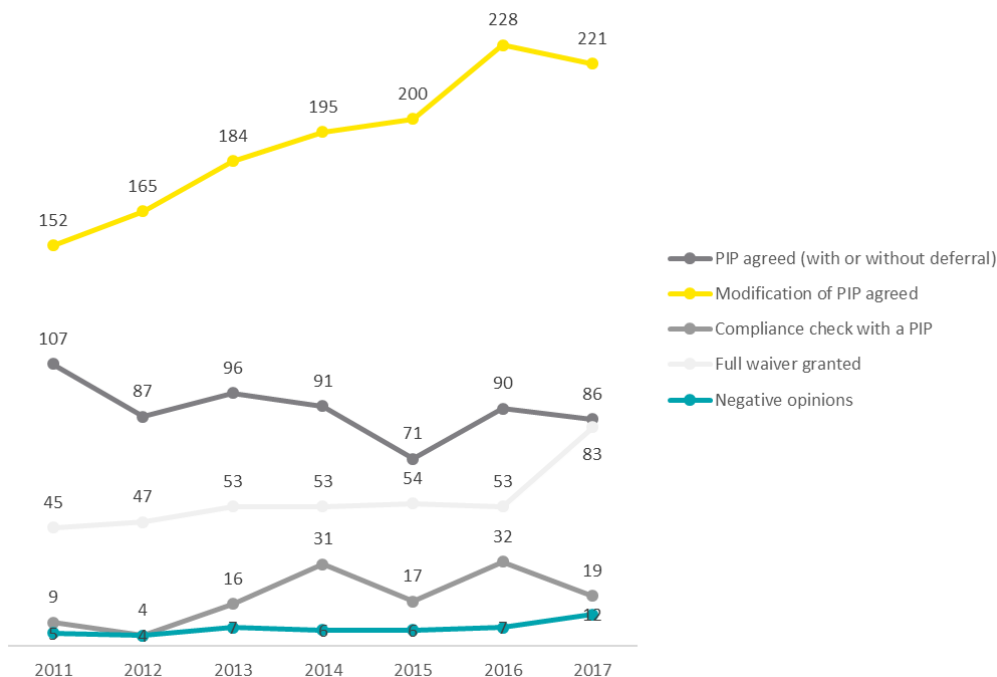
**The PDCO faces certain challenges, identified in the action plan on paediatrics.**

The main role of the PDCO is to assess the content of paediatric investigation plans (PIPs), which determine the manner in which companies must study the potential effects on children when developing a medicine. Each medicine going through the marketing authorisation procedure needs to include the results of studies as described in the PIP. As knowledge increases throughout the development, PIPs can be modified. Exceptions are made for medicines that are granted a deferral (delayed studies) or waivers (medicines not relevant for children). Next to agreeing on PIP (with or without deferrals) with the applicants and granting waivers, the regulatory authorities also conduct compliance checks, to ensure the agreements presented in the PIP are upheld.

The number of PIPs agreed by the PDCO has increased over the past years. The same holds for the number of full waivers granted. Negative opinions, whilst remaining marginal, have also increased over the study period.

<sup>57</sup> EMA, Annual Reports 2010-2017

**Figure 31: Opinions on paediatric investigation plans and waivers<sup>58</sup>**



The 2018 action plan on paediatrics identified five topic areas which needed to be addressed to contribute to a more effective functioning of the PDCO, notably:

- ▶ *Identifying paediatric medical needs*
- ▶ *Strengthening of cooperation of decision makers*
- ▶ *Ensuring timely completion of PIPs*
- ▶ *Improving the handling of PIP applications*
- ▶ *Increasing transparency around paediatric medicines*

Experts involved in the PDCO identified similar challenges with the procedure. Firstly, around 10 of the experts involved in the PDCO noted that as work on PIPs was not associated with fees, the resources allocated by NCAs are lower than in other areas. This leads to experts either having an exceptionally high workload or not being able to dedicate sufficient time to the work. Overall, the PDCO does not seem to have the same importance and regulatory apparatus backing it as other committees. Industry stakeholders have pointed out that there is no possibility to consult with the PDCO at an early stage, as a pilot project for early interaction has been discontinued by EMA, allowing for no interactive communication between the applicant and the committee. Whilst pre-PIP submissions are possible, they do not provide a platform for exchange. This leads PIPs being modified during the process, leading to unnecessary administrative burden. At the same time, earlier exchange between the PDCO and the applicant may allow the applicant to identify the potential incoherencies between CHMP scientific advice and PDCO requirements mentioned in sub-section 3.1.1 at a sooner stage and react accordingly.

A second point put forth by around 5 experts noted that the PIP template included some excess complexity and could be simplified. The complexity of the PIPs was put forth by around 10 experts as a reason that these were often not completed within the timeframes, hampering the overall process. A further piece of evidence highlighting the complexity of PIPs is the fact that PIPs are frequently changed throughout the process. The Commission report on the State of Paediatric Medicines in the EU from 2017 states that even though the number of amendments to the PIP decreasing, the average PIP is still modified at least once throughout the process.

<sup>58</sup> EMA, Annual Reports 2010-2017



As the identified shortcomings are reflected in the European Medicines Agency and European Commission action plan on paediatrics, it will be important to ensure the implementation of the action plan.

#### Product Case Study 4: RAPIBLOC

RAPIBLOC is indicated for the treatment of supraventricular tachycardia and for the rapid control of ventricular rate in patients with atrial fibrillation or atrial flutter in perioperative, postoperative, or other circumstances where short-term control of the ventricular rate with a short acting agent is desirable. The procedure was started in 2014. The PDCO submitted an opinion in September of 2014, and the PIP was agreed on in 2014. The date for completion was set for July 2018.

In 2016, the applicant submitted a proposed change to the PIP, which was reviewed by the PDCO. A modified PIP was accepted, the date of completion remained unchanged. In April 2018, the applicant again submitted proposed changes to the PIP. The PDCO refused the proposed modification in July 2018. The applicant brought to the attention of the PDCO that some aspects had not been assessed, leading to the PDCO considering a revision of its opinion. The revision started in July 2018 and led to a modification in timelines. The date for the completion of the PIP was set to December 2021.

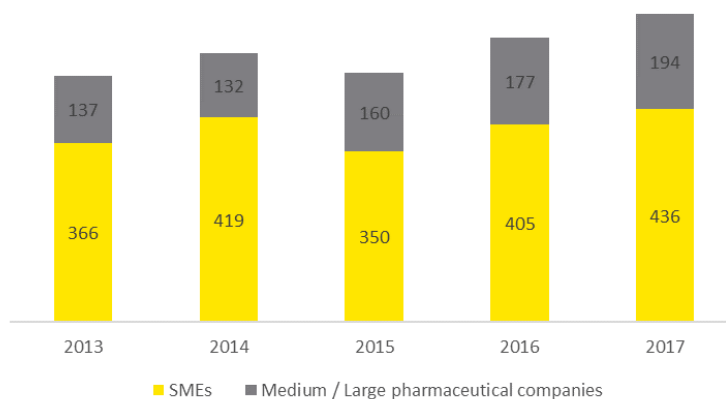
The case study presents an example where PIPs can pose a burden, with frequent revisions being necessary.

#### 4.1.3. Focus has increased on providing additional support to SMEs over the study period both at central and national level

##### The majority of scientific advice requesters at EMA level were SMEs.

SMEs consistently accounted for around 70% of all requesters at EMA level between 2013 and 2015, as illustrated by the figure below.

Figure 32: Scientific advice by affiliation of requester<sup>59</sup>



To address the unique needs of SMEs, the EMA Secretariat set up a dedicated SME office. The office was set up through Commission Regulation (EC) No 2049/2005 of 15 December 2005. Its aim is to promote innovation and development of new medicines for human and veterinary use by SMEs, through providing regulatory, financial and administrative assistance. The office provides six concrete services to SMEs:

1. Assignment of SME status<sup>60</sup>

<sup>59</sup> EMA, Annual Report 2017

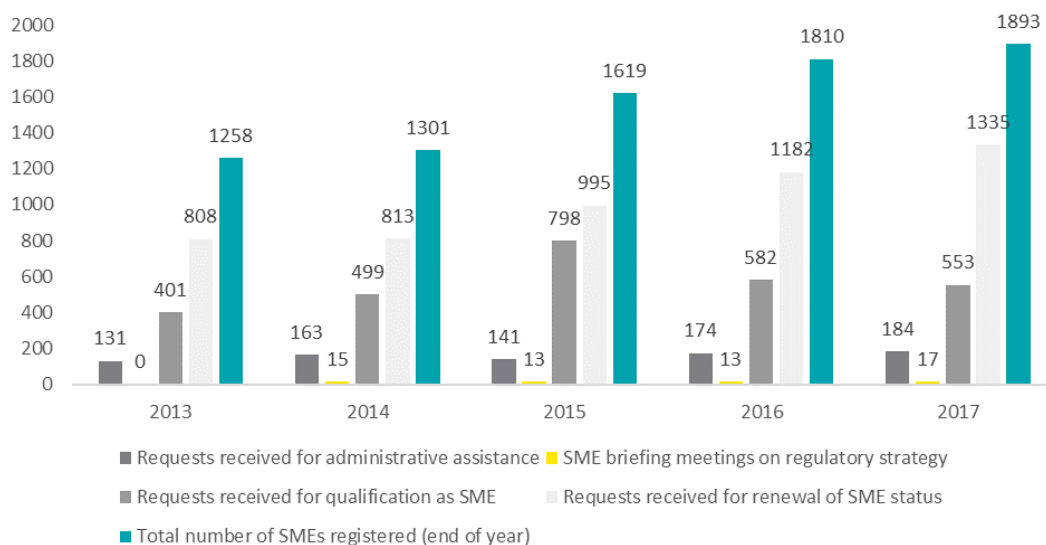
<sup>60</sup> To benefit from the support of the SME office, a company needs to receive SME status. This is done via the SME Office. An applicant must submit the Declaration on the qualification of an enterprise as a micro, small or medium-

2. *Regulatory Assistance*<sup>61</sup>
3. *Fee Incentives*<sup>62</sup>
4. *Translation Assistance*<sup>63</sup>
5. *Training and Awareness*<sup>64</sup>
6. *Partnering & Networking*<sup>65</sup>

**SME involvement has continually increased over the past years.**

The number of companies registered as SMEs as well as the relevant requests have increased annually since 2013. In 2013, there were 1,258 companies registered as SMEs with EMA, by 2017 this number had increased to 1,893. It is important to note that these figures include human and veterinary medicines.

**Figure 33: SME-related activities - Requests received (Human and Veterinary)**<sup>66</sup>



78% of NCAs agreed that EMA pre-authorisation activities were accessible for stakeholders including academia and SMEs. In addition, certain Member States e.g. Germany and Denmark ensured that support was in place for SMEs providing them with tailor-made assistance to address their needs. However, whilst SME support was identified as growing, completing an application successfully can still be an obstacle for some SMEs due to their complexity, costs and accessibility. This was confirmed both

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sized enterprise (SME) and fulfil the requirements according to Commission Recommendation 2003/361/EC. Once approved, the applicant will receive a registration number and must perform annual reporting requirements.

<sup>61</sup> SMEs can address administrative, regulatory and procedural queries to the office via mail. The office organizes SME briefing meetings as a platform for early dialogue between EMA and the SME. These meetings are free of charge and can be held in person or via telephone.

<sup>62</sup> The SME Office provides various fee incentives, including reductions, exemptions or deferrals. These incentives apply to scientific advice, post-authorisation activities, inspections, and marketing authorisation applications.

<sup>63</sup> The Office provides assistance with the translation of product information and opinion annexes, at no cost to the SME applicant.

<sup>64</sup> The Office organises info days and published a variety of information materials, such as newsletters, announcements, and user guides.

<sup>65</sup> Through the Office, a SME Register is set up, which facilitates and promotes interaction, partnering and networking between SMEs. It also serves as a source of information both for SMEs and their stakeholders as well as EU institutions, agencies and Member States.

<sup>66</sup> EMA, Annual Reports 2013-2017

through the open responses of NCAs as well as through the interviews conducted during the case studies in e.g. Germany and Denmark. It is further supported by scientific literature, as Amaouche et al. (2018)<sup>67</sup> find that SMEs still experience challenges in the quality and clinical sections of their marketing authorisation application, due to a lack of human and financial resources.

**At a national level, there are divergences in approaches in relation to the provision of pre-submission support.**

The Member State Case Studies found that in general, most Member States have some type of pre-submission mechanisms in place, such as the innovation offices in Germany or Spain. However, some Member States seemed to put a greater focus on accompanying the industry at an early stage in comparison than others. This divergence can lead to unequal opportunities for the receipt of early stage advice at national level, with divergences therefore existing in the type and quality of advice provided.

**Advice received at a national level is regarded as useful by both NCAs and industry stakeholders.**

Stakeholders noted that advice provided by NCAs at national level is less costly and less formalised than that provided by EMA. This allowed for more open discuss interactive discussions. This can be particularly valuable for smaller companies, especially SMEs, with less expertise on EMA procedures. These companies might find it easier to contact the NCA first and discuss a potential product in a familiar national setting. A successful example of this can be found in Spain, which has undertaken large investments in facilities for ATMPs. This has led to Spain being a leader in clinical trials for ATMPs and academic work being further pursued in SMEs. The NCA has an active innovation office that is in contact with SMEs, further developing the national ATMP industry.

**Since early stage advice is provided both on national and European level for all types of procedures, there is a need for coordination.**

Concerning coordination among network actors in relation to early stage advice, there is potential to improve communication and cooperation between NCAs and the EMA Secretariat in relation to the provision of early advice to companies. EMA maintains that national advice can help, especially in the beginning of the process, as smaller companies may be more familiar with the national environment. NCAs consulted during the case studies however reported that EMAs activities were expanding. This is supported by the Strategic Reflection of EMA on Regulatory Science to 2025, which calls for an increase and expansion of early stage outreach to academia and SMEs. However, NCAs consulted during the case studies strongly believed that early stage advice is better done at national level. This can lead to potential 'territorial conflicts' between EMA and NCAs, thus rendering early stage advice less effective by leading to a potential duplication of work. Room for improvement was identified in relation to pre-submission activities for the DCP and MRP.

**Managing advice from various NCAs can be difficult for companies.**

For instance, where the requests are submitted in parallel and the outcome is not completely superimposable, complications can exist with a difficult implementation of different recommended approaches. The handling or pre-submission activities can vary depending on the RMS, with feedback from industry representative identifying both cases where pre-submission meetings were accessible and instances where this was not the case.

**An important problem was mentioned regarding over-the-counter (OTC) medicines.**

Standards across Member States can vary greatly with Member States either disagreeing on whether a product can be designated as an OTC or employing different requirements regarding e.g. claims. As OTC status falls into national competencies, when it comes to the switch from prescription to OTC, pharmaceutical companies currently have to liaise with each of the NCAs involved prior to the submission of the dossier to find out about the specific requirements.

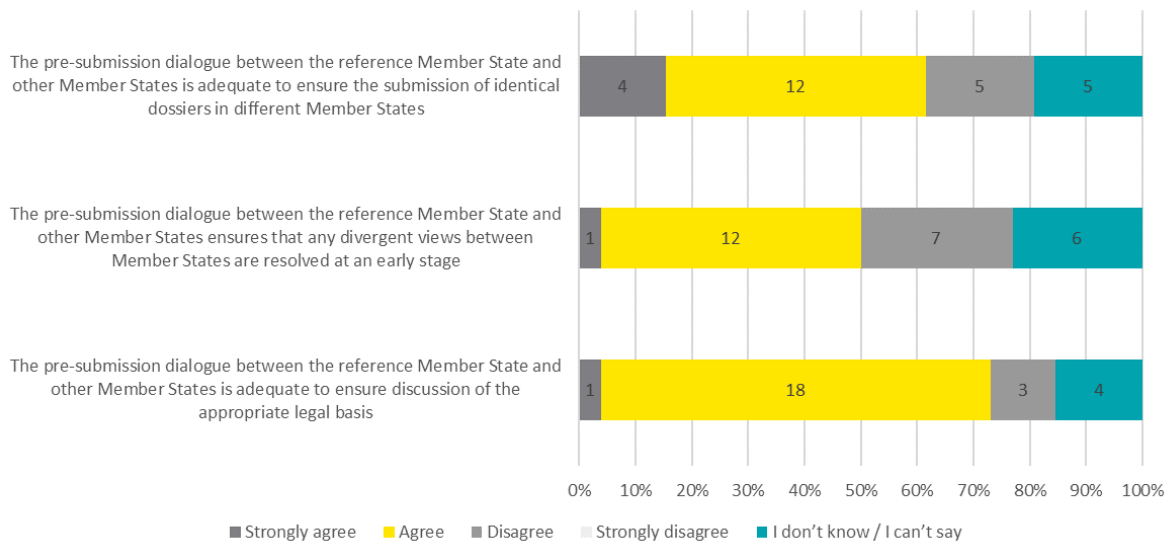
**Pre-submission dialogue between NCAs is interpreted differently.**

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<sup>67</sup> Amaouche, N., Salomé, H. C., Collignon, O., Santos, M. R., & Ziogas, C. (2018). Marketing authorisation applications submitted to the European Medicines Agency by small and medium-sized enterprises: an analysis of major objections and their impact on outcomes. *Drug discovery today*, 23(10), 1801-1805.

75% of NCA respondents agreed that dialogue between the reference Member States and the other Member States at the pre-submission stage is adequate to ensure the submission of identical dossiers in different Member States. They noted that it lies within the responsibility of the marketing authorisation applicant to ensure dossiers are identical. However, half of NCAs considered that dialogue does not ensure the resolution of divergent views. This does not pose a problem, as pre-submission activities are not foreseen as a stage to discuss and solve diverging views. Furthermore, disagreements regarding the legal basis are usually solved at the CMDh. Nonetheless, 3 NCAs note that non-formalised pre-submission dialogue takes place in case of very complex cases and is deemed useful by NCAs.

**Figure 34: In relation to the decentralised and mutual recognition procedures, to what extent do you agree with the following statements?**



Source: Expert Survey, CMDh Respondents

61% of CMDh respondents to the online survey considered the pre-submission dialogue between the reference Member State and other Member States to be adequate to ensure the submission of identical dossiers in different Member States. 19% of respondents (5 experts) disagreed with this. These respondents noted that since dossiers are submitted simultaneously via Common European Submission Portal (CESP) to all Member States, and therefore they are considered identical. Regarding the subject matter, 50% of CMDh respondents also considered that the pre-submission dialogue between the reference Member State and other Member States ensures that any divergent views between Member States are resolved at an early stage, with 27% (7 experts) disagreeing with this. Moreover, 73% of respondents from the CMDh considered that the pre-submission dialogue between the reference Member State and other Member States is adequate to ensure discussion on the appropriate legal basis, with three disagreeing with this statement. However, those that disagree with the two latter statements note that this is usually solved during the validation process, which seems to work well.

Interviews for case studies with NCAs identified that issues can exist in some instances in ensuring the submission of identical dossiers. However, respondents at NCAs during the case studies indicated that in most instances bilateral communication ensured any issues were resolved, with NCAs identifying the improvement over time based on experience and practice.

## 4.2. Do pre-submission activities support the achievement of the objectives of the EU regulatory framework for medicinal products in terms of innovation and competitiveness?

### 4.2.1. New approaches to contribute to innovation and competitiveness

To ensure that the network's activities are up to date with innovation and ensure overall competitiveness with other markets, several approaches have been adopted by the network over the study period. These approaches and mechanisms succeed in supporting the general objective of establishing a regulatory framework that favours competitiveness. Whilst these approaches vary in form and standing, this section presents three prominent examples:

- ▶ **PRIME:** a scheme recently launched based on provisions of the law;
- ▶ **The Innovation Task Force:** a group with scientific, regulatory and legal competences to provide a forum for early dialogue on innovation;
- ▶ **Adapted Pathways:** a pilot project on early and progressive patient access.

**PRIME provides the Network with a new tool to support competitiveness and innovation.**

The Priority Medicines (PRIME) scheme was initiated in March 2016 by EMA. The objective of the scheme was to enhance the support for the development of medicines that target and unmet medical need, speeding up their authorisation process. The launch of PRIME followed a consultation of stakeholders including the European Commission Expert Group on Safe and Timely Access to Medicines for Patients (STAMP) and mobilised the European Regulatory Network as a whole.

The eligibility criteria for PRIME are quite specific<sup>68</sup> as it is limited to medicines under development, which have not been authorised in the EEA and which are eligible under the centralised procedure for a marketing authorisation. Products eligible for PRIME aim to address unmet medical needs, which means that the product presents a specific public interest in terms of either diagnosis methods, prevention or treatment of a condition.

In addition, products are eligible for the PRIME Scheme provided that the product demonstrates a potential to address the unmet medical need by maintaining and improving the public health at the EU level by introducing new methods of therapy or by improving existing ones.

Based on the applicant, the request to benefit from PRIME can be initiated at various stages of the development phase of the product.

- ▶ In general, sponsors can submit a request to benefit from PRIME provided that it is engaged in the clinical trial phase of the product's development. Preliminary clinical evidence must be available, in order to establish the product's potential to address unmet medical needs. This data constitutes the proof of concept
- ▶ In more exceptional cases, both applicants from the academic sector and SMEs can submit to benefit from PRIME at an earlier stage, provided that the applicant is able to base the request on compelling data which are evidence of a promising activity (proof of principle) or that the applicant is able to present first in man studies which indicate exposure to the expected therapeutic effects.

The eligibility request to PRIME is to be reviewed by the Agency. The first step of the review will look to confirm that the request enters the defined scope. Once it is established the request falls under the scope for PRIME scheme, it will be examined by the Scientific Advice Working Party (SAWP). Should the product fall under the definition for ATMPs, a review by the CAT will also be conducted.

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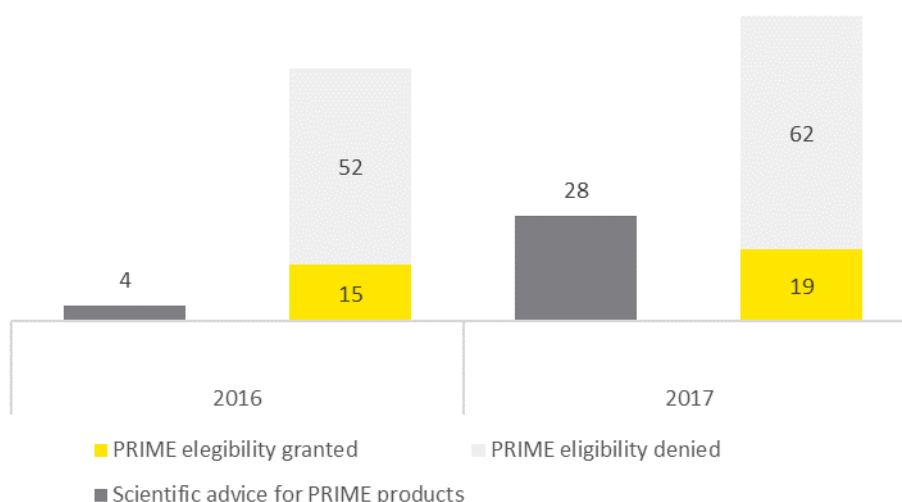
<sup>68</sup> European Medicine Agency – European Medicine Agency Guidance for applicants seeking access to PRIME scheme

Should the applicants be granted benefit from the PRIME scheme, they will become eligible for scientific advice and accelerated assessment once the marketing authorisation process, which is under the centralised procedure, is initiated.

In order to better target the necessary clinical trials, sponsors benefiting from PRIME will have access to early dialogue and scientific advice. In 2016 and 2017, a total of 32 products which applied for PRIME eligibility requested scientific advice, with the large majority doing so in 2017.

The PRIME scheme eligibility was accorded to 15 medicines (out of 67 requests) in 2016 and 19 medicines (out of 81 requests) in 2017. Half of the applicants are SMEs. The medicines concerned mainly oncology, haematology-haemostaseology, neurology and endocrinology-gynaecology-fertility-metabolism.

**Figure 35: PRIME scientific advice and eligibility<sup>69</sup>**



The PRIME scheme was welcomed by the pharmaceutical industry as a procedure which allowed the EMA to respond to similar procedures put in place by the USA and Japan. The sentiment that PRIME was part of a necessary process to ensure EMA keeps up with global development was also shared by NCAs. The procedure presented a welcome opportunity to reflect on how MAPs could be developed in the future. Despite the success of the procedure, 3 NCAs interviewed during the case studies noted that the ultimate goal of marketing authorisation procedures was not ensuring speedy procedures, but rather ensuring the safety of patients. It needed to be considered that with the current level of resources, procedures such as PRIME can only be successfully implemented in certain cases.

The general opinion presented in the expert survey differed slightly. Of the 10 experts specifically mentioning PRIME in the open question, half agreed that it is good procedure that should stay limited to the specific case of addressing unmet medical needs, whilst the other half called for its expansion to other products as well. These considerations however have to take into account the Ombudsman inquiry, further detailed in sub-section 4.3.3. Patient organisations raised the same point, that very close interaction between the pharmaceutical industries and the authorities posed a potential challenge to regulatory independence, which needed to be kept in mind.

**The ITF complements the efforts of national innovation offices on a European level.**

Established within EMA more than 10 years ago, the Innovation Task Force (ITF) unites several experts from various disciplines and fields of expertise. Based on the Mandate of the EMA Innovation Task Force, the ITF’s role is to provide support to medicines innovation and to focus in particular on Emerging Therapies and Technologies.

<sup>69</sup> EMA, Annual Report 2017

The main task of the ITF is to provide opportunity for applicants, and for SMEs in particular, for an informal dialogue, which is independent from the market authorisation procedure and which must be distinguished from pre-submission meetings.

Meetings with the ITF are aimed to allow the applicant identifying any issue, either legal, regulatory or scientific, which will potentially affect the product's development.

From a procedural point of view, the ITF can also discuss the issues potentially arising from eligibility to various procedures conducted by EMA.

The ITF has been working informally with the innovation offices of the NCAs since 2011. The cooperation was formalised in 2015, by creating the EU Innovation Network, of which the ITF is part of. The aim of the network is to make regulatory support for medicine developers more visible and attractive. It does this by sharing experiences and best practices, facilitating contacts between industry and regulatory agencies, identifying emerging trends and contributing to consolidating EU expertise. According to EMA statistics of 2014, 50% of ITF requests come from academia whilst 33% come from SMEs.

13 out of 16 NCAs stated that the role of the ITF is clear and appropriate and that it provides added value to the system. The finding is supported by 8 out of 9 experts. The only challenge mentioned was the need for increased communication both externally to raise awareness among stakeholders as well as internally to ensure coherence with national innovation offices within the EU Innovation Network.

**The Adapted Pathways pilot showed good initiative from EMA but was less successful in its implementation.**

EMA ran a pilot project on adaptive pathways from 2014 to 2016 to explore the practical implications of the concept. The adaptive pathways approach is a scientific concept of medicines development and data generation. It aims to facilitate early and progressive patient access to medicines by trying to balance timely access for patients with the need to provide adequate information on the benefits and risks of the patients.

In the EU, the adaptive pathways approach builds on the conditional marketing authorisation, combining it with the experience gained from introducing various post-marketing monitoring tools through the reform of the pharmacovigilance system. A central characteristic of adaptive pathways is the involvement of all relevant decision makers across the life-span of the medicine.

The pilot project was built on three principles:

- ▶ **Iterative development**, meaning either approval in stages or a conditional approval based on early data;
- ▶ **Gathering evidence** through real-life use to supplement clinical data;
- ▶ **Early involvement** of patients and HTA bodies

The pilot received 62 applications. Whilst 18 proposals were held before face-to-face meetings, the majority did not qualify for reasons such as the development programme not affording scope for expansion, proposals addressed areas without unmet needs or development programmes already being in a late stage. Of the 18 face-to-face meetings, 6 applicants received parallel advice from EMA and HTA bodies, whilst one applicant benefited from EMA's scientific advice. The others did not progress beyond initial discussions because subsequent scientific advice cast doubt on the feasibility of the development plan. Towards the end of the project in December 2016, EMA hosted a stakeholder workshop to discuss the approach as well as planning potential next steps.

The pilot presented several key conclusions, namely that the approach can foster multi-stakeholder development and can help include the requirements of said stakeholders upfront, whilst at the same time not being suitable for the development of all products. Should the project be developed further, the involvement of patients and healthcare professionals, the post-authorisation data gathering plans and the involvement of paying MS organisations remain issues that need to be addressed. Especially the involvement of patients and healthcare professionals was mentioned during interviews, with stakeholders calling for more transparency and more publicly available information on the procedure.



#### 4.2.2. Outreach to foster innovation has increased

##### **Various steps at a pre-submission level have been taken to increase competitiveness and innovation.**

EMA has taken the initiative to implement measures to boost competitiveness, such as the above-mentioned PRIME, going beyond the requirements of the legislation. There are existing Committees, notably CAT, that are focussed on fostering innovative medicines. SME involvement has also increased, with the number of SMEs registered increasing continuously over the past years. The increased efforts of EMA in the field of innovation is also evidenced by the EMA Strategy 'Regulatory Science to 2025', which includes the goal of enabling and leveraging research and innovation in regulatory science. Outreach to academia has also increased, although the perception of some industry stakeholders remains that NCAs and EMA could more actively help develop research. In this aspect the same stakeholders considered that the FDA is more active in reaching out towards innovators, whilst EMA has procedures in place that require innovators to take the first step.

##### **Both NCAs and industry stakeholders have pointed out that pre-submission activities performed by the U.S. Food and Drug Administration (FDA) are more flexible and quicker.**

An NCA interviewed during the case study pointed out that scientific guidelines tend to be developed and updated quicker by the FDA than EMA. Research-based industry stakeholders positively mentioned the flexibility and continual support provided by the FDA, which allows closer interaction prior to the submission of the application. This entices many innovative companies to develop new products on the US market before bringing them to the EU.

To increase competitiveness 2 NCAs interviewed during the case studies, industry stakeholders and around 3 experts have actively called for ensuring closer contact between industry and authorities during the pre-submission phase. To do so, they called for an enlargement of the scope of PRIME to ensure that close and flexible regulatory support is accessible to a large part of the industry. However, EMA pointed out that the potential perception of bias is a greater challenge in Europe due to the various stakeholders involved. This requires that formalised procedures are in place. The same sentiment was echoed by patient and consumer organisations and needs to be considered against the background of the Ombudsman inquiry discussed in 4.3.3.

### 4.3. Do pre-submission activities support the achievement of the objectives of the EU regulatory framework for medicinal products in terms of quality of subsequent scientific outputs and safety for patients?

#### 4.3.1. Scientific guidelines are key for providing high-level advice but could be enhanced further

##### **Scientific guidelines ensure the clarity of information for marketing authorisation applicants.**

General pre-submission guidelines are considered to be sufficiently clear and subject to regular updates. The pharmaceutical industry stakeholders consulted noted the clarity and usefulness of the guidelines. The same sentiment was shared by the NCAs with 95% finding that the scientific guidelines were clear to some extent. 88% of experts considered the scientific guidelines developed by EMA to be clear for potential applicants with the remainder not being in a position to comment on their clarity.

As an example, the pilot tailored biosimilar Scientific Advice procedure guidance was initially perceived as insufficiently clear at the time of launch, with the lack of clarity acting as a deterrent for companies to engage. Following a first attempt to receive clarification through questions and answers, a further dialogue opportunity was provided by EMA in the Spring of 2018 which allowed industry to provide input into the process. A number of practical industry proposals were consolidated for EMA's consideration

with a view to enhancing predictability and efficiency of the procedures as well as to ensure the procedure is 'fit-for-purpose' for biosimilar medicines developers.

Even though general opinions of the guidelines were high, some inefficiencies have been identified:

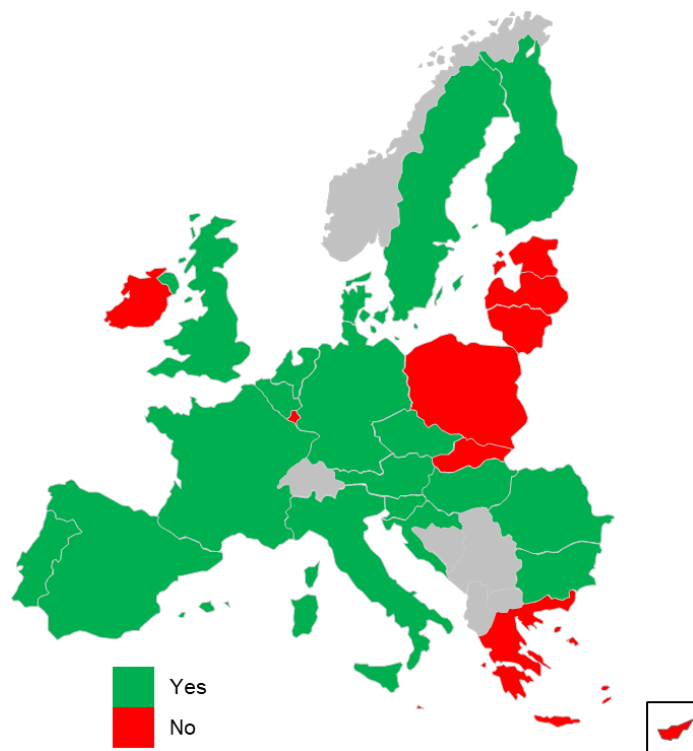
- ▶ **Review:** Due to the large number of existing guidelines, a periodic review of all guidelines is needed to ensure they are still relevant and up to date. Currently, guidelines do not have a shelf-life or a compulsory review after a certain period. For rapidly evolving technologies, this would be necessary on a more frequent basis to ensure novel technologies are included as soon as possible, a point that was highlighted by EMA and confirmed by NCA experts.
- ▶ **Innovation:** Currently, research-focused pharmaceutical industries have noted that guidelines can at times be slow to adapt to innovation and new developments. Guidelines are normally drafted once sufficient experience is available within the system, not making use of early-involvement of academia in the elaboration of guidelines, which could help create guidelines on new developments more quickly. Early-stage consultation of external experts, especially academics, could speed up the development of certain guidelines, which in turn would address industry needs and ensure higher availability of information.

#### 4.3.2. The system shows flexibility regarding patient safety and unmet needs

##### **NCA's can implement programmes in which they can grant patients access to a drug that has not yet been authorised.**

These so-called 'compassionate-use' programmes allow patients with life-threatening, long-lasting or seriously debilitating illnesses quick access to medicines that have not yet completed the authorisation process. Whilst the safety profile and dosage of the medicines may not be fully established, they must however be in the clinical trial phase or have entered the marketing authorisation process. Compassionate use programmes are coordinated and implemented on a national level, with each Member State setting its own rules and procedures. As of 2016 18 Member States in the European Union had legislation in place to implement such a programme.

**Figure 36: Legislation on compassionate use programmes in EU Member States<sup>70</sup>**



<sup>70</sup> Balasubramanian, G., Morampudi, S., Chhabra, P., Gowda, A., & Zomorodi, B. (2016). An overview of Compassionate Use Programs in the European Union member states. *Intractable & rare diseases Research*, 5(4), 244-254.

Whilst the implementation of a compassionate use programmes is a national competency, according to Article 83 of Regulation (EC) No 726/2004, NCAs have to inform EMA if they make a product available to a group of patients. Furthermore, NCAs can ask EMA for an opinion on how to administer, distribute and use certain medicines for compassionate use. If this is the case, the CHMP will provide an opinion and also identify which patients might benefit. Over the study period, the CHMP has provided five opinions, two in 2010, two in 2013 and one in 2014.

**In addition to compassionate use programmes, there exist so-called ‘named-patient basis’ treatments.**

These allow doctors to obtain a medicine directly from the manufacturer. These processes are done on an individual basis and do not need to be reported to EMA. When compared with the US system, the European system provides a clearer legislative definition, as the FDA does not distinguish between named-patient basis and compassionate use.

Overall, the implementation of compassionate use is regulated sufficiently to ensure the safety of patients. Patient organisations interviewed did not criticise the programme, and whilst there are no consolidated numbers available, in Member States such as Germany, Netherland, Austria or the UK, the procedure is only used on average 3-5 times a year. This shows that it seems to be successful in providing a measure of last resort, without undermining the normal authorisation procedures.

#### 4.3.3. Close cooperation between EMA and industry stakeholders is under critical regard

**In 2017, the European Ombudsman opened an ‘inquiry into the pre-submission activities that the European Medicines Agency (EMA) offers to individual medicine developers.** The inquiry was conducted at the initiative of the Ombudsman. The inquiry was opened against the background that close cooperation between medicine developers and EMA during the pre-submission phase may pose a risk that eventual marketing authorisation decisions by EMA may be influenced by this cooperation. Furthermore, even if decisions remain objective and complete, the risk of potential bias in the eyes of the public persists, which in turn damages the reputation of the overall regulatory system in place.

EMA responded to the inquiry by stating that pre-submission procedures are well-established processes globally and are essential for the quick and efficient development of medicines, whilst also acknowledging the need to avoid risk and manage potential bias. EMA stated that the necessary safeguards are in place, separating the advice function from the final decisions process. The risk of bias is further decreased by the fact that final approval decisions are taken in a committee, hence no single person has a final say. The European Ombudsman made a decision in July 2019<sup>71</sup>, which found that EMA should carefully manage the contacts its evaluators have with medicine developers during the pre-submission phase. Furthermore, EMA should provide greater transparency on its pre-submission activities. In light of these findings, the necessity for EMA to continue to implement pre-submission activities in a strictly formalised manner is evident.

#### 4.3.4. Despite different approaches, international cooperation exists, increasing global safety measures

**EMA has formalised its working relations with a number of international regulators through bilateral confidentiality agreements.**

These agreements focus on exchange of information, both of regulatory as well as safety-related nature. More importantly, the EU has signed mutual recognition agreements (MRA) with a number of third countries. This notably include mutual recognition of good manufacturing practice (GMP) inspections. These agreements aim to facilitate market access and international harmonisation. The EU has entered into MRAs with Australia, Canada, Israel, Japan, New Zealand, Switzerland and the United States. The agreements are complemented by joint inspections of manufacturing sites of common interest, which helps rationalise GMP inspections at an international level and fosters cooperation and mutual confidence. These efforts, together with those undertaken by the EU in the scope of the International

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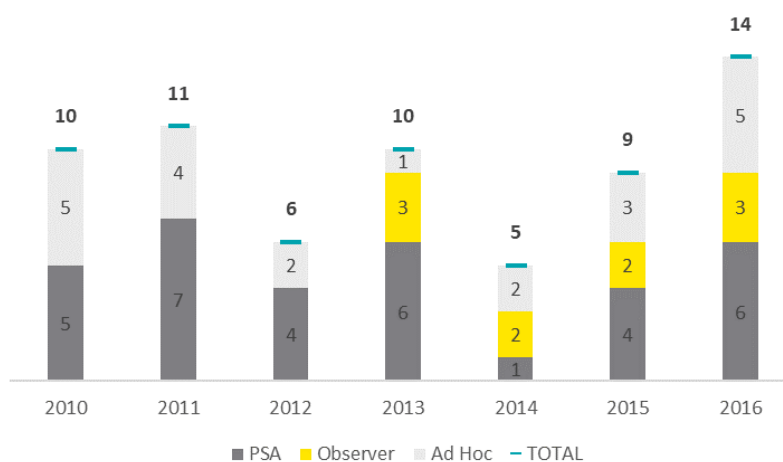
<sup>71</sup> European Ombudsman (2019). OI/7/2017/KR – Decision in strategic inquiry OI/7/2017/KR on how the European Medicines Agency engages with medicine developers in the period leading up to applications for authorisations to market new medicines in the EU

Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), contribute to an increased harmonisation of global safety standards.

**In an effort to increase and ensure the safety of patients globally, EMA is cooperating with regulatory authorities outside of Europe.**

For example, EMA and the FDA have implemented a parallel scientific advice programme (PSA), which offers applicants to interact with both agencies at the same time to optimise development for both markets. The programme was started in 2003, however uptake of the study period was low, with only 14 applicants in 2016. In light of the low uptake, which is attributed to lack of awareness, perceived process challenges, preference to discuss with Agencies separately, and the level of convergence, the **General Principles of PSA were reviewed in 2017**. The update includes a stronger focus on communication and sharing of information as well as a new element of consultative advice, where limited experts from either side are invited to participate in discussions of the other agency.

**Figure 37: EMA FDA Parallel Scientific Advice<sup>72</sup>**



#### 4.4. Are pre-submission activities efficient in terms of costs incurred from both the industry and the EMA network to achieve the expected output?

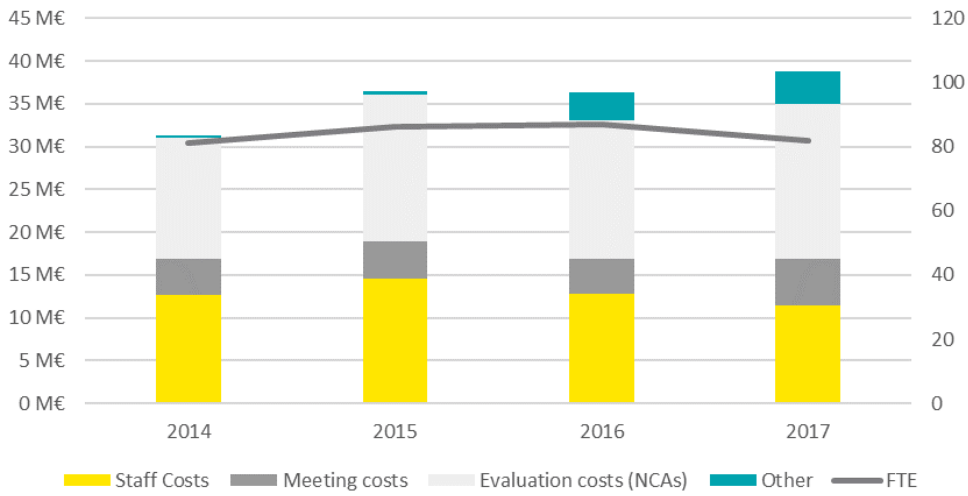
4.4.1. Expenditure on pre-submission activities has increased in line with the benefits achieved

**EMA expenditure on pre-authorisation procedures has increased, from EUR 31,3 million in 2014 to EUR 38,7 million in 2017.**

The expenditure, which covers all pre-authorisation activities including dedicated committees, rose in line with the increasing pre-authorisation activities of the agencies, which is evidenced for example by the rise in scientific advice requests. Over the same time period, staff numbers have remained relatively stable, with 81 in 2014 and 82 in 2017. It is interesting to note that costs associated with meetings have increased from EUR 4,2 million to EUR 5,4 million whilst staff costs have decreased from EUR 12,6 million to EUR 11,5 million. Whilst the evolution of staff costs is in line with the development of overall staff costs related to human medicines, meeting costs have increase more significantly.

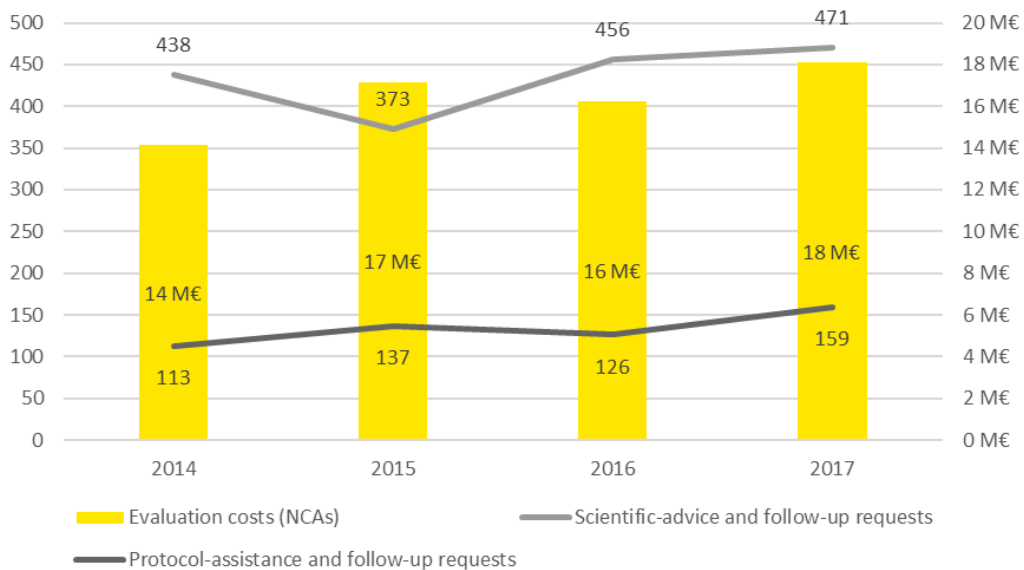
<sup>72</sup> Recent update of the guidance for Parallel EMA/FDA scientific advice (2017)

**Figure 38: Staff and expenditure – Pre-Authorisation activities (human)** <sup>73</sup>



Looking specifically at the evaluation activities, expenditure seems to have evolved in line with the number of activities undertaken, confirming the fact that efficiency has stayed constant.

**Figure 39: Evolution of evaluation costs and scientific advice requests** <sup>74</sup>

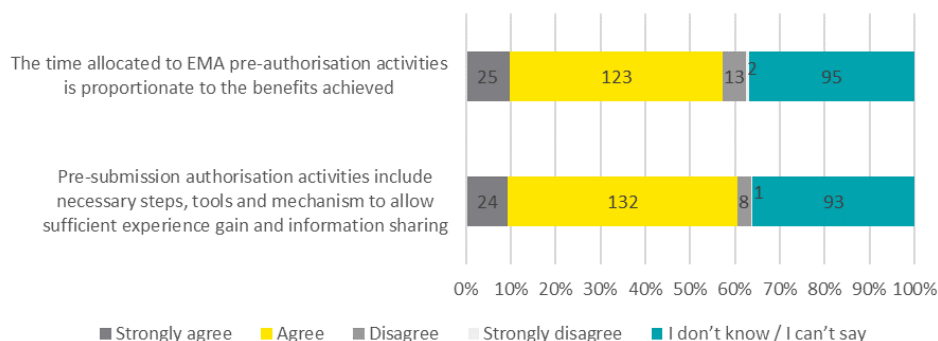


90% of experts either strongly agreed or agreed that the time allocated to EMA pre-authorisation activities to be proportionate to the benefits achieved, with an even higher proportion agreeing that they include all the necessary steps for efficient functioning.

<sup>73</sup> EMA, Annual Activity Reports 2014-2017

<sup>74</sup> EMA, Annual Reports 2014-2017 & Annual Activity Reports 2014-2017

**Figure 40: To what extent do you agree with the following statements about pre-authorisation activities?**



Source: Expert Survey

#### 4.4.2. Overlaps or little cooperation between certain parties can lead to a loss of efficiency

##### **Committee cooperation plays an important role in ensuring the efficiency of pre-authorisation activities.**

The 2010 study made reference to the need to ensure that there are no major inconsistencies between scientific advice on the one hand and PDCO and CHMP opinions on the other. According to the EMA Secretariat, significant efforts were undertaken to ensure this is the case by facilitating discussions between the SAWP and other committees such as CAT, COMP and PDCO. Around 10 experts mentioned this positive development in the survey as well, unprompted. At the same time, the Secretariat aims to increase communication between committees responsible for pre-authorisation activities such as PDCO and COMP and CHMP. The finding was shared by the pharmaceutical industry, which confirmed that in general, there were no inconsistencies between the scientific advice provided and the committee opinions. Whilst some examples were mentioned where the opinions of PDCO and CHMP diverged (see 3.1.1), these presented exceptions to an overall well-functioning exchange.

##### **As mentioned in the previous sections, there are instances where early scientific advice activities between EMA and the NCAs overlap.**

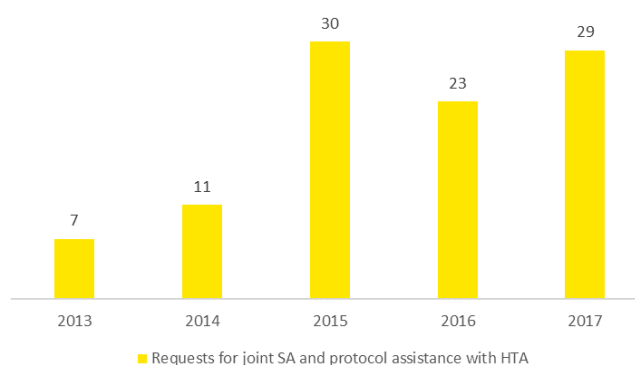
Whilst this can hamper the overall effectiveness of the system if responsibilities are not clear, it also provides a general inefficiency. When looking at the system as a whole, some activities risk being duplicated, hence resources being allocated twice. Closer coordination could thus eliminate the duplication of effort at the general level.

##### **There are efficiency gains possible regarding coordination with HTA bodies.**

Whilst EMA has no remit in decisions on pricing and reimbursement, cooperation with HTA is nonetheless beneficial, as it facilitates mutual understanding of the decision makers across processes. Collaboration has been started both at EU and national level.

- ▶ On the **EU-level**, EMA is collaborating with the European Network for Health Technology Assessment (EUnetHTA) to offer applicants simultaneous, coordinated advice on their development plans. This initiative was started in 2010 and has since developed, with the number of joint procedures per year increasing over the past years. According to EMA, patients were involved in around two-thirds of the joint advice procedures.

**Figure 41: Requests for joint SA and protocol assistance with HTA<sup>75</sup>**



- ▶ At the **national level**, cooperation between the NCAs and national HTA bodies is offered but rarely used. A number of member states had the possibility of joint advice between NCAs and HTA bodies, however uptake differed. Whilst Portuguese stakeholders mentioned that this option was well received by the pharmaceutical companies, Swedish and Italian stakeholders noted that even though it existed, the option was rarely used by the pharmaceutical industry. This is in part due to the fact that the mechanism is being expanded at the European level, which presents a more attractive opportunity for the industry.

**Joint advice with HTA bodies provides a major efficiency gain.** For an applicant, non-coordination could in the worst case mean a product that has been authorised is not reimbursed, as the HTA authority does not see sufficient additional benefit, which essentially means that it will not be sold. If an applicant receives the input of the HTA body alongside the development of the application, the chance that the product will be allowed on the market is higher. However, despite the initial cooperation projects at the EU level through EUnetHTA, currently HTA bodies of the Member States do not have a harmonised approach. This is currently being addressed by a legislative proposal of the Commission, but over the study period, various types of industry stakeholders have indicated that receiving common HTA advice was difficult. This is in large part due to the fact that HTA has historically been a domain in which Member States apply their own procedures in assessing the technological and economic viability of a new medicinal product. Especially the latter point makes it's a sensitive subject, as reimbursement is related to national health budgets, a quintessential national competency. Thus, despite joint procedures existing, Member States are wary to move competencies to a central level, and subsequently joint assessments are not legally binding. This is evidenced by the fact that on average 6,6 Member States participated in Joint Assessments of EUnetHTA, but only 2,2 used it in direct decision making, thus providing little security to applicants. This security would be especially important for products going through novel, high-visibility procedures, such as PRIME. If a product going through all procedures is at the end not recognised by HTA bodies as sufficiently convincing to recommend reimbursement, the resources spent on the path of the product through Marketing Authorisation Procedures go to waste. Hence, closer cooperation is essential to increase overall efficient use of time and money.

#### 4.4.3. Pre-submission activities provide a significant efficiency gains for the system

**From a purely theoretical view, pre-submission activities provide an important contribution to the overall efficiency of the system.** Pre-submission activities are an input towards the specific objective of streamlining procedures as they increase communication between regulators and the industry. They allow applicants to better understand the needs and requirements of regulators, as well as the regulatory environment in general, allowing them to streamline the development, improve the design of clinical trials and ultimately increase the chances of obtaining sufficient data for the later application. It thus helps ensure no time or resources are wasted on performing invalid or incorrect studies. At the same time, regulators are exposed to the product at an early stage, providing them time to familiarise themselves with the subject matter and better prepare for the later procedures. On a general level, this

<sup>75</sup> EMA, Annual Report 2017



exchange increases data quality and thus ultimately the efficiency and effectiveness of the decision process.

## 5. Work Package 3: Initial Marketing Authorisation Procedures

The aim of this Work Package is to examine the extent to which initial marketing authorisation procedures<sup>76</sup> effectively and efficiently support the achievement of the network's regulatory objectives, especially in terms of fostering competitiveness and ensuring patients' swift access to reliable and innovative medicines whilst allowing rationalisation and simplification of the system.

In detail, this section aims to answer five questions:

1. Are initial marketing authorisation procedures suitable and effective to deal with all types of applications and medicines?
2. Do initial marketing procedures allow a swift access to medicinal products for patients?
3. Do initial marketing procedures support the competitiveness of the European Pharmaceuticals sector?
4. Do initial marketing procedures allow the marketing of reliable products?
5. Have initial marketing procedures been successful in ensuring a reasonable level of administrative burden? Are these procedures cost-efficient?

### Synthesis

The Centralised Procedure (CP), Mutual Recognition Procedure (MRP) and Decentralised Procedure (DCP) play a pivotal role in ensuring a high level of health protection for EU citizens by providing a swift access to reliable and innovative medicinal products whilst supporting the competitiveness of the European Pharmaceutical sector.

**The co-existence of different procedures is a strength of the EU current system**, which supports the competitiveness of the pharmaceutical industry within the EU:

- ▶ The different procedures are well-adapted to deal with existing types of medicines: the list of medicines for which the centralised procedure is compulsory is adequate, with a majority of new, innovative medicines passing through the centralised authorisation procedure in order to be marketed in the EU.
- ▶ The ability to choose between CP, DCP, MRP or purely national procedures is fully adapted to other types of medicines such as generics, for which the three main procedures provide a wide array of options for applicants. The CP provides a solid and robust procedure, which is preferred by research-based companies. This differs from MRP and DCP, which allow country selection where the choice for commercial and reimbursement decisions are generally considered.
- ▶ This system allows flexibility and is appealing for companies that know the pros and cons of the different types of MA and related procedures from both a theoretical and practical point of views.

**Initial marketing authorisation procedures overall comply with legally binding maximum regulatory deadlines.**

- ▶ The CP regulatory timeframe is appropriate and could hardly be shortened, given the specific environment in which it operates. Compared with other international regulators, the median approval time for new active substances by EMA is slower but remains adequate overall, with various mechanisms that allow quicker access to the market for some medicines. The industry

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<sup>76</sup> An outline of each of the steps of the three procedures can be found in the Annex, Section 10.1, page 157.

calls for even shorter deadlines and a wider use of accelerated procedures, but this does not clearly reduce EU competitiveness and most New Active Substances authorised globally are brought to the European Market quickly.

- ▶ Increased visibility of DCP and MRP timeframe would be welcomed given the high level of heterogeneity across MS.

**Initial marketing authorisation procedures provide for transparent and clear steps, but they require a high level of workload for experts and heavy procedural infrastructure with the EMA and the network**

- ▶ As the CP involves duplicate procedures and formal involvement of NCAs from all MS, it requires a lot of capacity, which the system has been able to deal with so far. However, in light of rising workloads, there is a need to focus on what is critical and complex, so as to not overburden the system. More specifically a differentiated approach could however be envisaged depending on the products, allowing CHMP to focus on first-in-class medicines, ATMPs and NCEs. Increased flexibility, more informal collaboration and simplified decision-making could be adapted for generics, which currently follow the same timelines as innovative medicines and represent a high workload for the CHMP. CP administrative burden could also be reduced by further exploiting the added-value of peer review (as all MS can comment anyway) and simplifying the assessment report templates.
- ▶ Regarding the DCP and MRP, procedures are less burdensome for the system, though less transparent, predictable and efficient for applicants themselves due to inconsistencies and an unharmonised application of the regulation across MS. The current MRP process allows countries to have additional requirements and administrative controls, leading to procedures being delayed in frequent cases.

**The three procedures include robust and consistent measures to ensure suitable and reliable products are marketed and guarantee a high level of health protection for EU citizens.** This also relies on the high level of scientific expertise involved within the Network, as well as the quality of delivered opinions (based on opinions and factual evidence), with benefit/risk assessment decisions that are also transparent to the public. The rapporteurship is allocated to the relevant experts, although it could be rendered more transparent.

## 5.1. Are initial marketing authorisation procedures suitable and effective to deal with all types of applications and medicines?

5.1.1. Whilst the global number of CP applications has stayed constant, there has been a decrease in DCP and MRP applications.

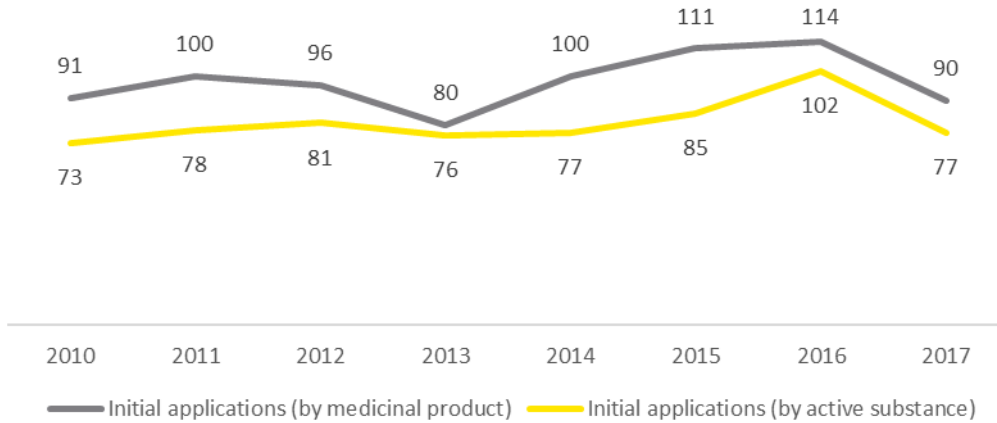
**For the centralised procedure, the number of initial marketing applications through the centralised procedure has remained relatively constant since 2007.**

The number of initial applications of medicinal products ranged at around 100 applications per annum, reaching a low of 80 applications in 2013 and a high of 114 applications in 2016. The number of applications by active substance<sup>77</sup> has followed a similar trend.

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<sup>77</sup> The active substance is the substance responsible for the activity of a medicine. Different products can have the same active substance, hence the variation in applications.

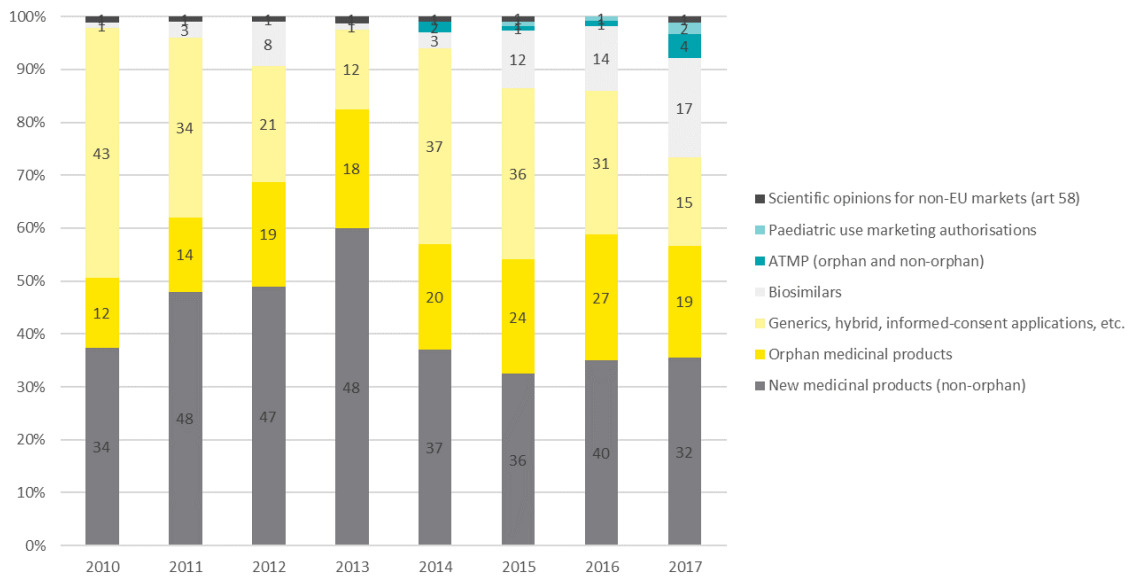
**Figure 42: Initial-evaluation applications<sup>78</sup>**



**The majority of products going through the CP are new and orphan medicinal products.**

Together, these two categories account for between 50% and 80% of all CP procedures. Generics account for around 30%, whilst the relative amount of Biosimilars and ATMPs has been growing over the past years.

**Figure 43: CP by type of product**

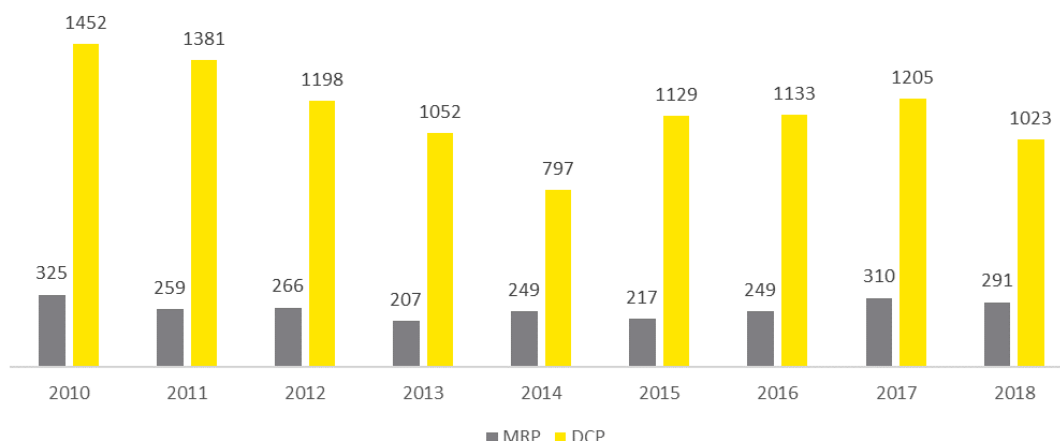


**The number of products falling under both the MRP and DCP have decreased over the study period.**

Whilst there has been a substantial decrease in DCP, from 1,432 in 2010 to 1,023 in 2018, the decrease in MRP has been slower, from 325 in 2010 to 291 in 2018. Over the study period, MRP reached its lowest point in 2013 at 207 procedures and DCP in the following year with 797 procedures.

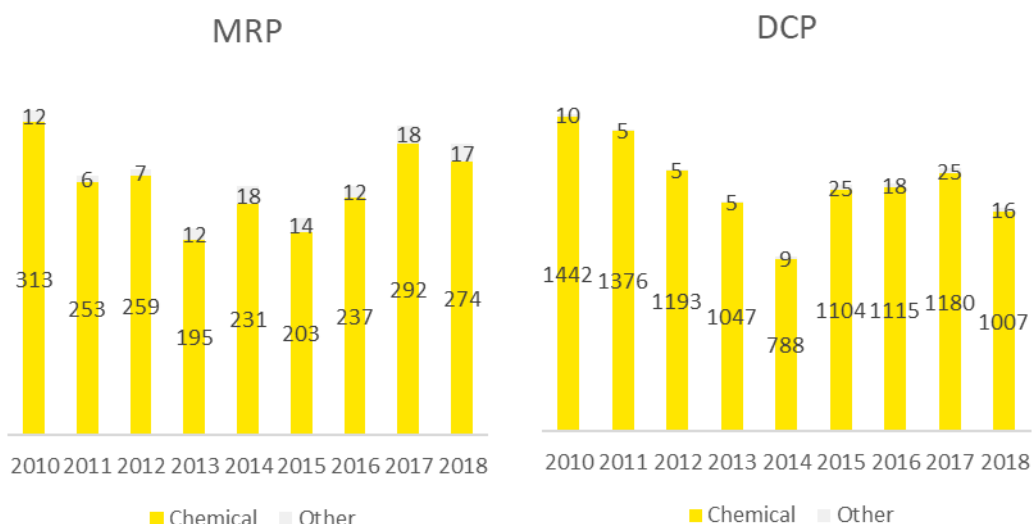
<sup>78</sup> EMA, Annual Reports, 2010-2017

**Figure 44: Evolution of MRP and DCP procedures<sup>79</sup>**



Chemical products account for over 95% of all MRP/DCP applications.

**Figure 45: MRP/DCP by type of product**



More detailed figures on the number of applications by type of medicine and procedure can be found in the Annex.

5.1.2. The complementarity of procedures is a strength of the European system, with the CP providing a robust option and the MRP/DCP more flexibility

**The marketing authorisation procedures are flexible to adapt to current needs.**

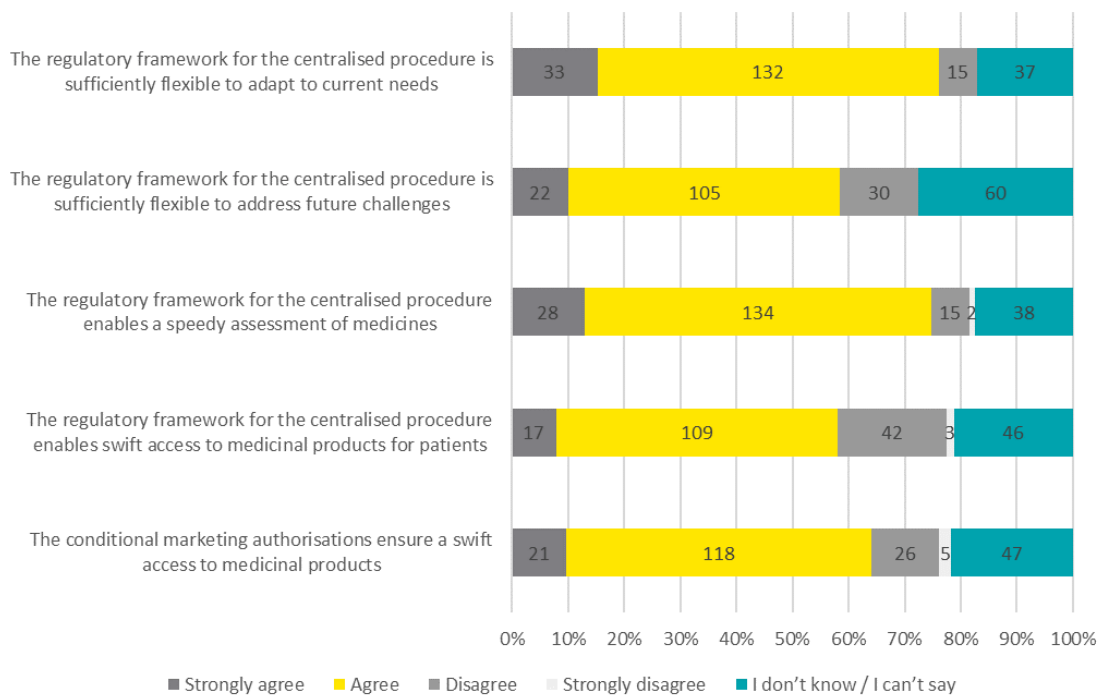
Pharmaceutical industry stakeholders interviewed valued the flexibility allowed by the combination of the three procedures. Putting aside the legislative requirements, the system allowed applicants to choose a suitable procedure based on speed, target markets, access costs and maintenance costs. All three procedures are complementary with clear criteria which provides the opportunity for marketing authorisation holders to apply a clear regulatory strategy to obtain a marketing authorisation in Europe. The CP provides a robust option, with a common procedure for all Member States and timelines that are clear and respected, whilst the MRP/DCP provides more flexibility for the applicant.

<sup>79</sup> HMA, Annual Statistics 2010-2018

This finding was supported by both experts and NCAs responding to the online survey and written questionnaire. 78% of experts either strongly agreed (16%) or agreed (62%) that the regulatory framework was flexible. Moreover, 76% of NCAs responding to the written questionnaire also agreed or strongly agreed that the regulatory framework for the centralised procedure is sufficiently flexible for current challenges.

For MRP/DCP this flexibility was confirmed by 76% of CMDh experts responding to the online survey that considered the regulatory framework to be sufficiently flexible to adapt to current needs. The flexibility to adapt to future challenges however requires some attention, as further detailed in section 5.1.4.

**Figure 46: To what extent do you agree with the following statements regarding the regulatory framework for the centralised procedure**



Source: Expert survey, all respondents apart from CMDh experts

**The centralised procedure is adequate to address the needs of most types of medicines.**

Whilst some products have decreased slightly in number of applications per annum, the constant trend over all medicinal products demonstrates the needs still being addressed by the centralised procedure for different types of medicinal products. The adequacy of the procedure was confirmed through responses to the online survey with 86% of experts responding to the survey considering the scope to be adequate to a high or some extent.

Pharmaceutical industry stakeholders interviewed specifically highlighted the clear structure and schedule it follows. Due to the legislative requirements, the centralised procedure is especially important for research based pharmaceutical companies. The importance of the CP is underlined by the fact that it is the required procedure for innovative products and products of high importance and potential added value to patients, such as orphan drugs and ATMPs. At the same time, multinational companies with sufficient expertise and resources in place also preferred this option, which shows that structural setup of the procedure is well received if resource constraints are not important.

**The MRP/DCP was considered as more flexible and adaptable.**

Industry stakeholders indicated that the benefits of the MRP/DCP are that it enables country selection which may be optimal in certain situations based on the specific type of product or company footprint. This was especially the case for generics, OTC and herbal medicines. Pharmaceuticals producing generic medicines may have an interest in using different product names for the same product,

according to the naming conventions in the various countries, which may be linked to pricing and reimbursement systems. Furthermore, the indication and prescription status of a medicines may differ between Member States, a circumstance to which the MRP/DCP is flexible enough to adapt to. Whilst industry stakeholders have noted that timelines are less strictly adhered to than the CP, the overall procedure is shorter and less costly.

**An interesting finding concerned the use of EU-level procedures as opposed to purely national ones.**

In some of the Member States investigated during the case studies such as Estonia and Sweden, purely national procedures diminished and pharmaceutical industry preferred CP or MRP/DCP. In other Member States such as Spain and Germany, this was not the case and national procedures remained consistently high. This shows that national circumstances such as market size may also have an effect on the overall preference of the procedures as the industry in some MS may be more familiar with the national procedure.

5.1.3. Whilst the CP is preferred by research-based companies, it is less suitable for generics whose producers tend to use the DCP

**The reasons for choosing the centralised procedure over the decentralised and mutual recognition procedure is primarily driven by the legislation.**

As presented in chapter 2, there are a number of products that are required to go through the centralised procedure. Looking beyond the mandatory scope, the choice of procedure depends on the commercial strategies of the pharmaceutical companies given and the type of product.

Data collected through Member State case studies found that the size of the company was a factor for choosing procedures, with the CP considered as daunting for smaller companies. As the CP systematically involves all MS, even if the product eventually might not be marketed in all MS, it can be more difficult to adapt a product according to the views of all Member States. At the same, the CP is more expensive than the MRP/DCP, especially if a product has multiple strengths, making it harder to access for companies with limited resources. This was particularly identified as a factor for Case Studies undertaken in smaller Member States with a smaller pharmaceutical market.

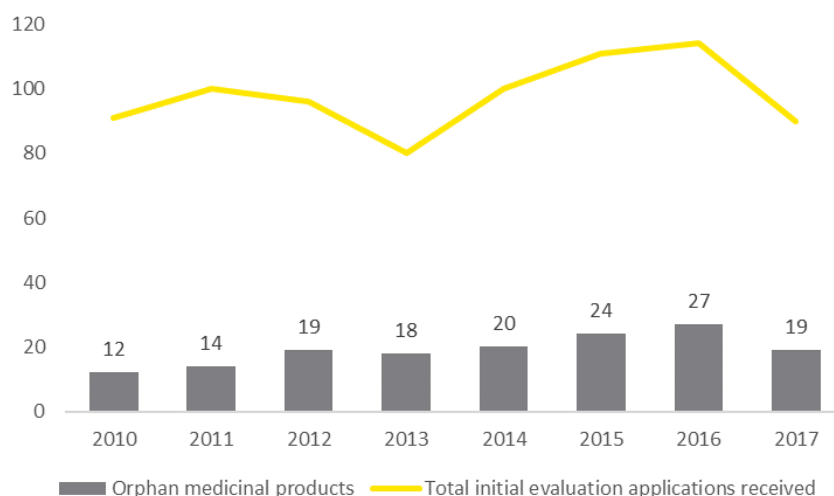
**The trends in the applications per type of product demonstrate the shift that has happened in the overall pharmaceutical market to more innovative products for the CP.**

For research-based industry stakeholders consulted through interview, the CP was considered as being significantly more systematic, with adherence overall to the timeline and a single marketing authorisation throughout the entire EEA making it the preferred approach in most scenarios for innovative medicinal products with a significant European footprint. NCAs consulted through Case Studies also confirmed that the centralised procedure provides a reliable and clear validation path for the medicinal product in question.

Both orphan medicinal products as well as ATMPs have experienced and increase over the study period. For orphan medicines, with the number of products increasing per annum from 12 in 2010 to 19 in 2017.

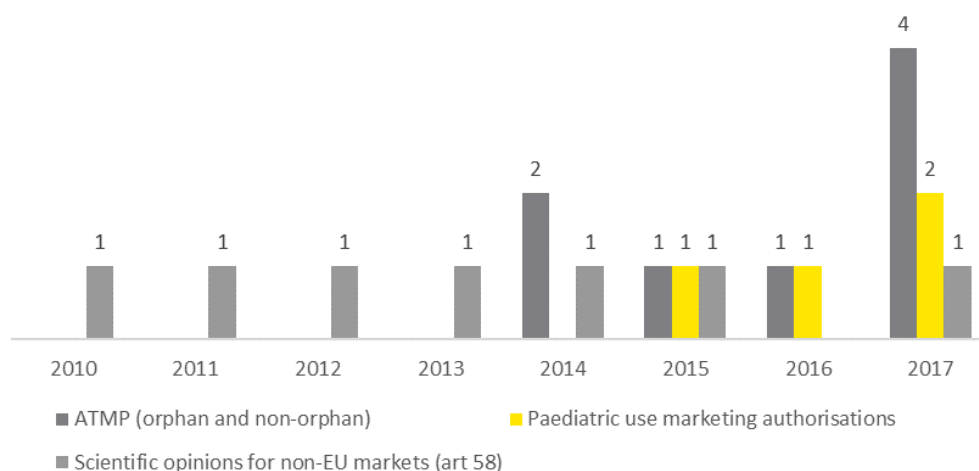


**Figure 47: Initial evaluation applications received – Orphan medicinal products<sup>80</sup>**



Regarding the applications for ATMPs, products for paediatric use and the scientific opinions for non-EU markets, the numbers remain low, as presented in the figure below. Whilst innovative products have witnessed an increase in number of applications, the low number of applications for ATMPs due to the fact that this is a nascent field and products are in development. This is supported by the rapidly increasing number of products being granted ATMP classification (see subsection 4.1.2).

**Figure 48: Initial-evaluation applications received – ATMP (orphan and non-orphan), Paediatric use marketing authorisations and scientific opinions for non-EU markets (Article 58)<sup>81</sup>**



### The MRP/DCP is more suitable for generics

The CP does not fulfil stakeholder needs regarding applications of generics, which do not fall under the mandatory scope. This is less due to the structure of the procedure, but rather due to differences in Member States. The CP limits the flexibility of applicants regarding issues such as product name, package sizes and indication. To illustrate the challenge, one can take the counterexample of ibuprofen and its indications, which is authorised via DCP. Whilst one MS may allow an indication for treating back pain, another may only allow migraine. Similar differences exist related to duration of use. If a generic

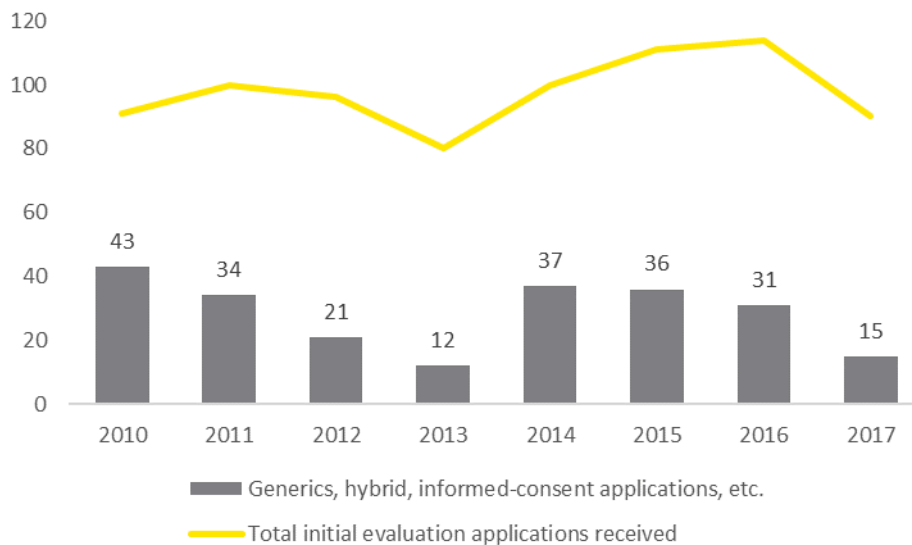
<sup>80</sup> EMA, Annual Reports, 2010-2017

<sup>81</sup> EMA, Annual Reports, 2010-2017

company goes via the CP, it is likely to have to adopt the opinion of the most conservative Member State, as the CP is consensus driven. The MRP/DCP allows different applications to choose Member States with indications that are more attractive for the industry. This means the industry can adapt the product according to the standards of each Member State and sell it with indications in some MS that would not be possible in other MS. A similar argumentation can be made for differences in pack size, prescriptions status and product name.

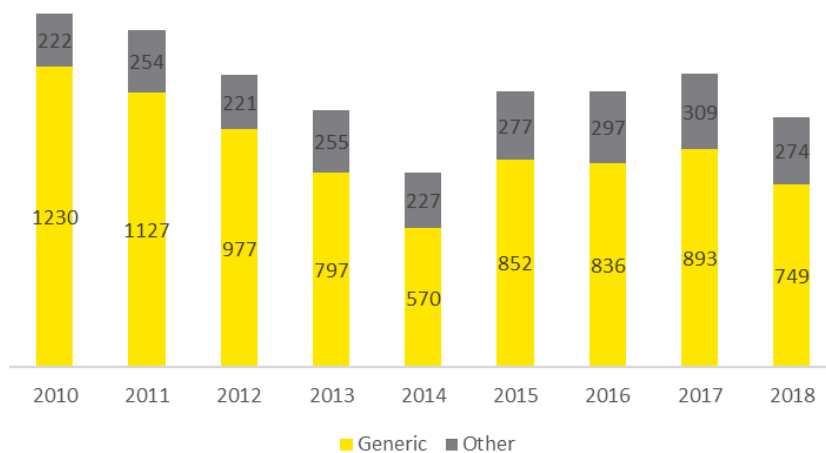
This is supported by a fall in the number of generic applications for the CP, from 43 in 2010 to 15 in 2017. In terms of percentage, generics fell from around 30-40% of CP applications to 20-30% of CP applications

**Figure 49: Initial evaluation applications received – Generics, hybrid, informed-consent applications etc.**<sup>82</sup>



At the same time, the proportion of generics for the DCP and MRP remained consistently high. For the DCP, generics constituted around 70-80% of applications per year.

**Figure 50: Generic applications DCP**<sup>83</sup>

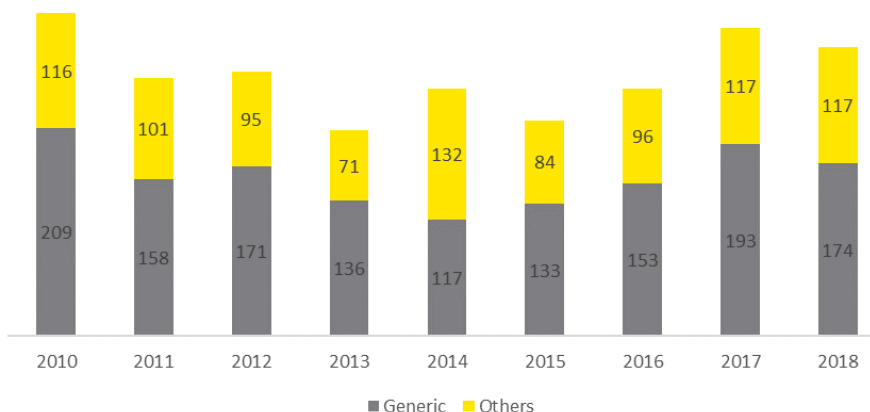


<sup>82</sup> EMA, Annual Reports, 2010-2017

<sup>83</sup> HMA, Annual Statistics 2010-2018

For the MRP, generics still accounted for the majority of products, although the percentage was slightly lower at around 60%.

**Figure 51: Generic applications MRP<sup>84</sup>**



#### 5.1.4. Obstacles were identified for certain product types

**The intersection between medicines and medical devices was identified as a future need that will need to be addressed.**

Currently, the authorisation of medicines and the authorisation procedure linked to medical devices are separate. Whilst the borderline area is covered by the existing regulatory framework, experts and NCAs interviewed noted that it is not very clear and effective. With products arriving on the market that are not easily put into one of the categories, the procedures will have to adapt to find tailored solutions.

**Both the CP as well as the MRP/DCP seem to be unfit for homeopathic and anthroposophic medicines.**

This is evidenced by close to 0 applications (there was 1 MRP application in 2018) for these procedures compared to the high number of products on the market. Currently, almost all products are authorised through national procedures. Industry stakeholders have noted that this is largely due to the administrative requirements of the procedure, which are necessary for all other types of products, but which seem unfeasible for these types of medicines which are brought to the market in much larger numbers than other medicines. Furthermore, acceptance of and expertise on these medicines varies greatly between Member States.

**Whilst the system is overall flexible to adapt to challenges, this often happens on an ad-hoc basis.**

The 2010 study concluded that the network should anticipate any significant evolution in the health domain and their impact on its activities, recommending that any potential impact of recent scientific evolutions should be explored through (i) launching a reflection on the middle-to-long term impact of personalised medicine concepts and (ii) launching a reflection on the need for specific competences at the CAT level to face the emergence of new products. Currently, the Scientific Committee Regulatory Science Strategy Division considers these aspects at EMA level, as evidenced by the Regulatory Science Strategy until 2025 document. However, there is no mechanism in place solely with the objective of identifying and addressing future challenges at network level. The ad-hoc nature of addressing rising challenges was confirmed by NCAs both through the questionnaire and the case studies. This can however create obstacles in relation to the system's overall flexibility to address future challenges. Whilst this may work in some areas, such as ATMPs, where expertise seems to be developing in line with their importance (despite capacity gaps still existing), other areas such as big

<sup>84</sup> HMA, Annual Statistics 2010-2018

data and digitalisation may require a more formalised action plan. This was a point highlighted by NCAs interviewed during the case studies and is also mentioned in the EMA 2020 strategy.

## 5.2. Do initial marketing procedures allow swift access to medicinal products for patients?

**Methodological note:** *When considering the extent to which initial marketing procedures allow a swift access to medicinal products for patients, the study primarily examined the extent to which the timelines for treating applications are respected for the procedures in question, the adequacy of these timelines and the extent to which access could be further improved. However, swift access is also associated with activities undertaken post-authorisation, such as activities undertaken by HTAs which are not falling within the scope of this study.*

### 5.2.1. The Centralised Procedure enables a speedy assessment of medicines, considering the complexity of the products in question.

**Considering the complexity of the products being examined, the timeline for assessment is appropriate.**

The 210-day timeline set out in the legislation provides an adequate framework from both a market-based viewpoint and a regulatory viewpoint. Pharmaceutical industry representatives expressed their overall satisfaction with the procedures, highlighting the robustness and timeliness as a clear strength. This was confirmed by 73% of experts considering that the regulatory framework for the centralized procedure enables swift access to medicinal products for patients. At the same time, the timelines allow the assessors to conduct a thorough assessment of the marketing authorisation application without incurring delays. The appropriateness of the timeline was observed through the Product Case Studies undertaken where the majority of products examined respected the timeline imposed for the centralised procedure.

The majority of experts (60%) as well as NCAs (71%) considered that the timelines should not be shortened. A further shortening of timelines could put the effectiveness of the system into jeopardy. The majority of NCAs consulted considered that their capacities were already stretched. They considered that the complexity of the applications has increased, with the evaluation requiring a greater number of experts and thus making the coordination of a coherent assessment and a professional assessment report more complicated. Any further pressure put on the system in terms of timeframes may thus, at a constant level of resources, have negative consequences on the overall functioning of the system.<sup>85</sup>

The extent to which the timeline could be shortened was also examined through interviews with stakeholders, with the majority of stakeholders consulted, regardless of their groups, considering that the timelines should be proportionate to the overall aim which is to ensure a high level of health protection for citizens.

#### Product Case Study 5: LAMZEDE

The examination of products falling under the centralised procedure through the product case studies highlighted the overall efficiency of the timeline with the majority of products respecting the regulatory timeline.

Some more complex products took more time, when examining specific cases. This was the case, for example in relation to Lamzede, designated as an orphan product for the treatment of alpha-Mannosidosis. The complexity of this product was seen through the lengthy pre-submission period which lasted for approximately six years.

Overall, excluding the clock-stop, the marketing authorisation procedure lasted 258 days, which is 48 additional days compared with the calendar provided by Article 6(3) of Regulation 726/2004. As with the pre-submission procedures, this was due to the complexity of the product requiring a tailor-made approach. This shows that whilst the large majority of products are authorised within the given

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<sup>85</sup> Finding based on feedback by NCAs collected through interviews

timeframe, there still exist products that take longer. At the same time, it shows the system is capable of adapting to address the requirements for complex products.

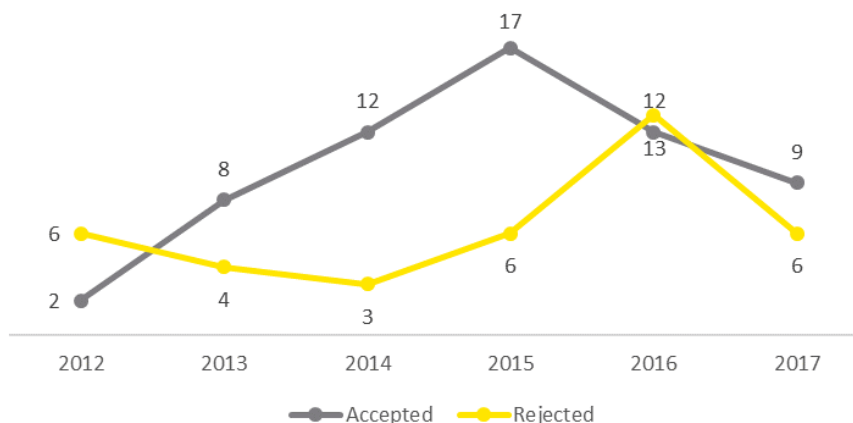
**The current system provides for two procedures that enable medicines to reach the market quicker, accelerated assessment and conditional marketing authorisation.**

Whilst the accelerated assessment speeds up the overall marketing authorisation procedure and delivers a final verdict at the end, conditional market provides a temporary marketing authorisation for one year, which needs to be re-assessed and potentially renewed after this period.

- ▶ The **Accelerated Assessment** procedure reduces the timeframe for the CHMP to review marketing authorisation applications. Products are eligible for this procedure if the CHMP decides that they are of major interest for public health and therapeutic innovation. There is no single definition of what constitutes major public health interest, thus the applicant has to justify it on a case-by-case basis, which is subsequently assessed by the CHMP. A justification can include the introduction of new methods or the improvement of existing methods both of which address unmet needs for maintaining and improving public health. Under the accelerated assessment, the time for evaluating applications is reduced from 210 to 150 days if the applicant provides sufficient justification. The accelerated assessment reduced the initial assessment phase from 120 to 90 days and the assessment of the responses to the List of Questions and the List of Outstanding Issues to 30 days each.

The number of accelerated assessment requests accepted during the study period has grown over the study period. The trend of requests accepted has shifted over the reference period, with 2012 seeing 75% of requests rejected. This can be compared to 2015, where 73% of requests were in fact accepted in that year. The trend has now balanced, with almost half of requests accepted in 2016 and 60% accepted in 2017. According to EMA the changes are in part due to the optimisation of the procedural framework, which among other things promoted early dialogue between regulators and applicants. This addressed the fact that previously the main reasons for rejection were the unmet medical need not being adequately justified and the dossier not being mature enough.

**Figure 52: Accelerated assessment requests<sup>86</sup>**



Although concerns were raised by selected NCAs and experts that the benefits of the accelerated procedure could be outbalanced by the risk on safety for patients, appropriate safeguards are in place. In challenging cases, the system puts the focus on patient safety, as evidenced by accelerated assessment procedures which were reverted to normal timelines due to lack of evidence or capacity.

<sup>86</sup> EMA, Annual Reports, 2012-2017

### Product Case Study 6: KANUMA

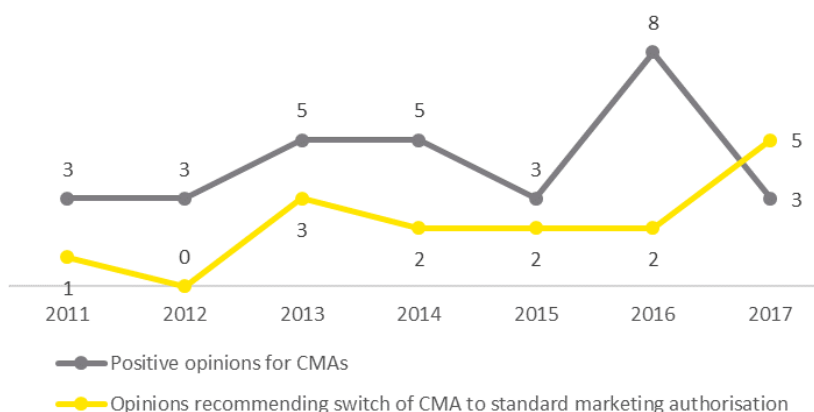
The product was designated as an orphan medicine on 17 December 2010. The applicant received Protocol Assistance from the CHMP on 19 July 2012. The Protocol Assistance pertained to quality, non-clinical and clinical aspects of the dossier. The accelerated assessment procedure was agreed-upon by CHMP on 20 November 2014, and the procedure started on 24 December 2014.

During the authorisation procedure, CHMP and PRAC successfully coordinated. The accelerated assessment procedure lasted 154 days, which is 4 additional days compared with the calendar provided by Article 14(9) of Regulation 726/2004. Overall, despite the minor delay, the case study showed that accelerated assessment procedures are implemented successfully, further underlined by the fact that all 5 PSUSAs conducted after the authorisation resulted in the PRAC recommendation of maintenance.

- ▶ The **Conditional marketing authorisation procedure** aims to support the development of medicines that address unmet medical needs of patients. A product receives a conditional marketing authorisation if the benefit of immediate access outweighs the risk of less comprehensive data. Whilst applicants applying for conditional marketing authorisation are encouraged to apply for the accelerated procedures, the default conditional marketing authorisation procedure follows the standard timeline of 210 days. To be granted a conditional marketing authorisation by the CHMP, the product must meet all the following requirements:
  - A positive benefit-risk balance
  - Likelihood that the applicant will be able to provide comprehensive data
  - Unmet medical needs
  - The benefit to public health of the medicinal products immediate availability on the market outweighs the risks due to the need for further data.

During the study period, 20 medicinal products received a conditional marketing authorisation, as outlined by an EMA report on CMA in 2016. None of these conditional marketing authorisations were revoked or suspended during the study period. Conditional marketing authorisation is believed to be a valuable tool for seriously debilitating or life-threatening diseases, emergency situations or orphan indications for which there is a positive benefit-risk balance on available data and unmet medical needs are fulfilled.

**Figure 53: Conditional marketing authorisation and switch to standard marketing authorisation<sup>87</sup>**



<sup>87</sup> EMA, Annual Reports, 2011-2017

### 5.2.2. The timelines for treating applications in the centralised procedure are respected

**For the centralised procedure, the regulatory timeframes have been respected in all or in the vast majority of cases.**

Performance and workload indicators between 2014 and 2017 indicated a 99% to 100% success of applications evaluated within regulatory timeframes. The average number of days for positive opinions has remained relatively constant, with the average assessment phase ranging between 157 days in 2009 to 202 days in 2015. With the Commission post-opinion phase, the average time taken by EMA for initial marketing procedures never exceeded 211 days (value of 2013).

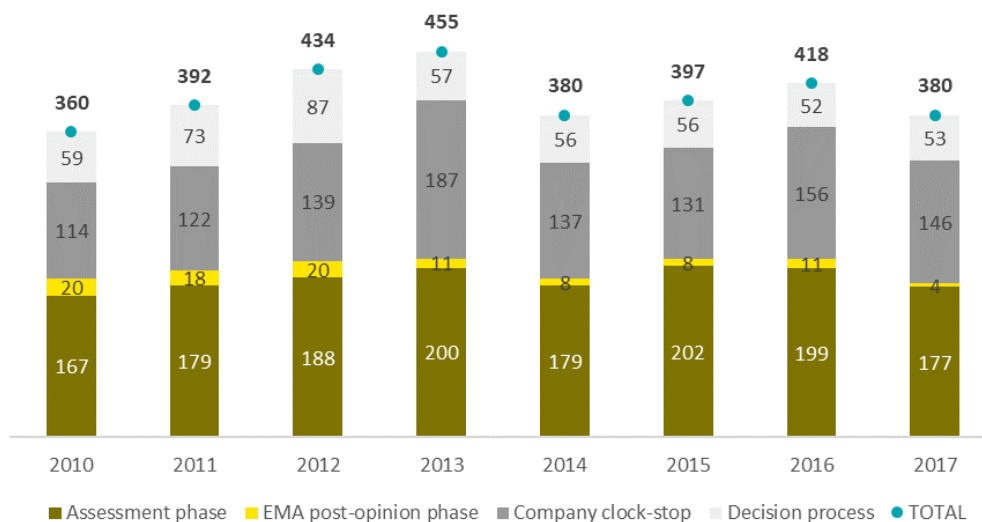
#### Product Case Study 7: ENTRESTO

The examination of ENTRESTO, a product indicated for the treatment of heart failure, demonstrates the contribution that pre-submission activities can make to ensuring the overall reliability and suitability of products. For this product, the pre-submission process lasted for approximately 5 years overall with long-term support provided by the CHMP.

When the marketing authorisation application was made in November 2014, the CHMP issued a positive opinion in 128 days, 82 days in advance of the overall time limitation. The rapidity of the marketing authorisation can demonstrate the positive contribution the pre-submission activities made to the overall assessment and the extent to which the marketing authorisation procedure in its entirety contributes to ensuring reliable and suitable products through the investment of resources prior to the submission of a marketing authorisation application.

Whilst the overall assessment period is in line with the regulatory timeframes, the company clock-stop time fluctuated more significantly, between 114 in 2010 and 187 in 2013. The average time taken for the Commission decision process ranged between 33 days in 2007 and 87 days in 2012, with the average lying above the pre-defined 67 days only in 2012 and 2013. Overall, the initial authorisation process through the centralised procedure took on average between 346 days (2009) and 455 days (2013).

**Figure 54: Average number of days for centralised procedures – positive opinions<sup>88</sup>**



### 5.2.3. Timelines under the DCP/MRP tend to be shorter, but are not respected as thoroughly

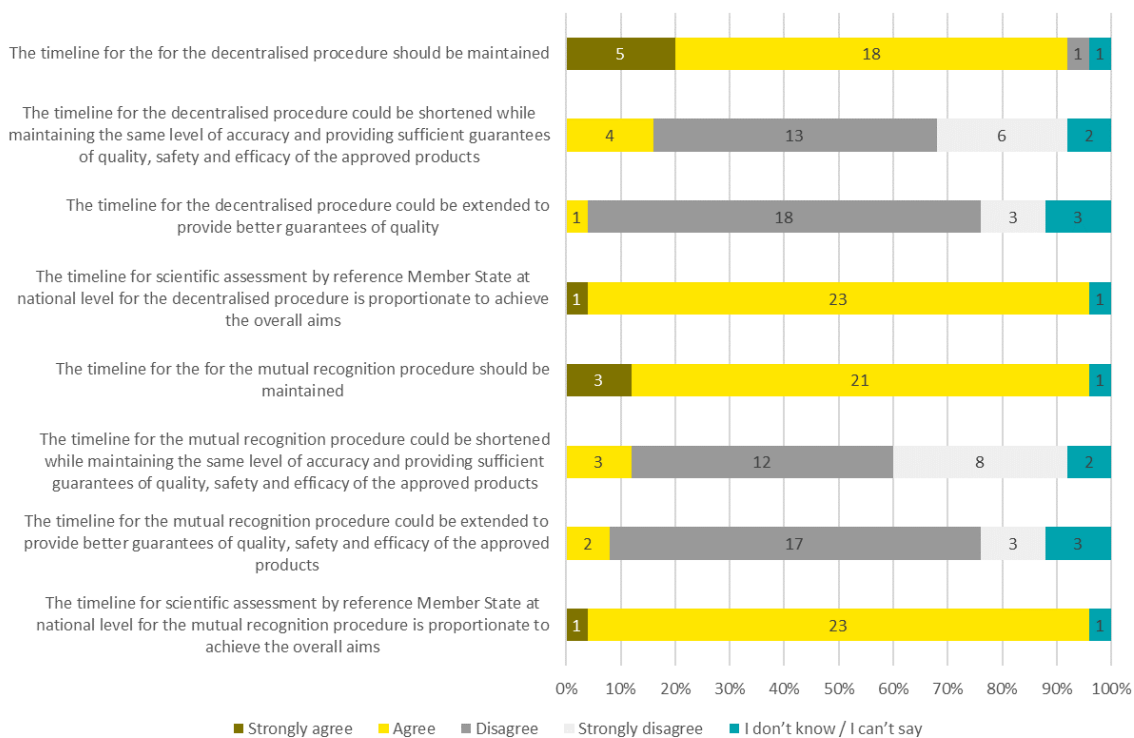
**Whilst the timelines for the DCP/MRP procedures are adequate and provide swift access for patients, they were not as rigidly respected as those of the CP.**

<sup>88</sup> EMA, Annual Reports, 2010-2017



In this regard, diverging views can be identified by different groups of stakeholders. For the DCP and MRP, 88% of CMDh experts responding to the online survey considered the regulatory framework to enable swift access to medicinal products for patients. 92% of CMDh respondents considered that the timeline for the DCP should be maintained, with 96% supporting this for the MRP. 78% considered that the timeline could not be shortened for the DCP, with 80% considering it not to be possible for the MRP

**Figure 55: With regard to timelines for the DCP and MRP, to what extent do you agree with the following statements?**



Source: Expert Survey, CMDh respondents

**Whilst DCP/MRP timelines are generally quicker, they can include a higher administrative burden.**

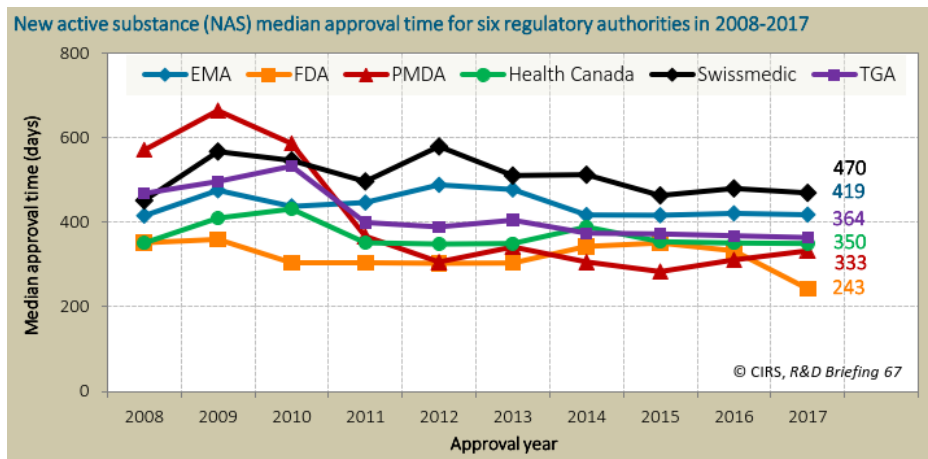
Representatives from the generics industry noted that DCP and MRP generally tend to be quicker procedures. However, industry organisations consulted also identified a higher level of administrative burden in comparison to the centralised procedure. One industry representative interviewed indicated that after an MRP/DCP application, a lack of clarity exists of the timing for when the national marketing authorisation will be granted. In general, the timelines for these procedures are less respected than for the centralised procedure due to the delays that can exist in undertaking the assessments at national level. This was considered by the industry representative in question to be an obstacle to innovation to meet patients’ needs as it is difficult to plan when the medicine could be placed on the market.

**5.2.4. EMA approval times are slower than other international regulators regarding new active substances**

**Compared with other major medicines regulatory authorities across the western world, EMA has one of the longest median approval times.**

According to the Centre for Innovation in Regulatory Science (CIRS), in 2017 approvals of new active substances (NAS) by EMA took on average 419 days, including clock stops. However, the approval time is calculated from the date of submission to the date of approval, thus including both agency and company time (and in the case of EMA, Commission approval time). The figure below, from the CIRS R&D Briefing 67, compares the median approval time of six major regulatory agencies: EMA, the US FDA, the Japan Pharmaceuticals and Medical Devices Agency (PMDA), Health Canada, Swissmedic and the Australian Therapeutic Goods Administration (TGA).

**Figure 56: Comparison of approval times<sup>89</sup>**



**Despite the differences, median approval times across the six agencies are converging.**

According to Bujar et al. (2018), the difference between the slowest and fastest agency is 137 days, excluding the FDA. The outlying value for the FDA is explained by the fact that more than 60% of the FDA's approvals are expedited, which compares to around 40% of PDMA approvals and between 0% and 20% of the approvals of the other agencies. The length of EMA's processes can also be explained by the distinct regulatory environment in which it operates. Due to its multinational setting, EMA is the only agency that requires the decision of another authority (Commission decision) after its decision. In 2017, the median Commission decision time was 60 days. If this system-based factor were not to be taken into account, median EMA approval times would be in line with those of most other agencies.

**EMA expedited procedures are the second-fastest among the five agencies<sup>90</sup>.**

According to Bujar et al. (2018), this is likely due to the revision of the guidelines for Accelerated Assessment and may even further increase through the expansion of PRIME. Another important factor is the company response time, which is around 4x faster than under normal procedures, compared to the EMA review time being around 1.5x faster.

**Figure 57: Median expedited approval time 2017<sup>91</sup>**



**Whilst the overall approval time of products may take longer through EMA than most other regulatory agencies, the European system seems to be more robust and reliable when it comes to the timeframe.**

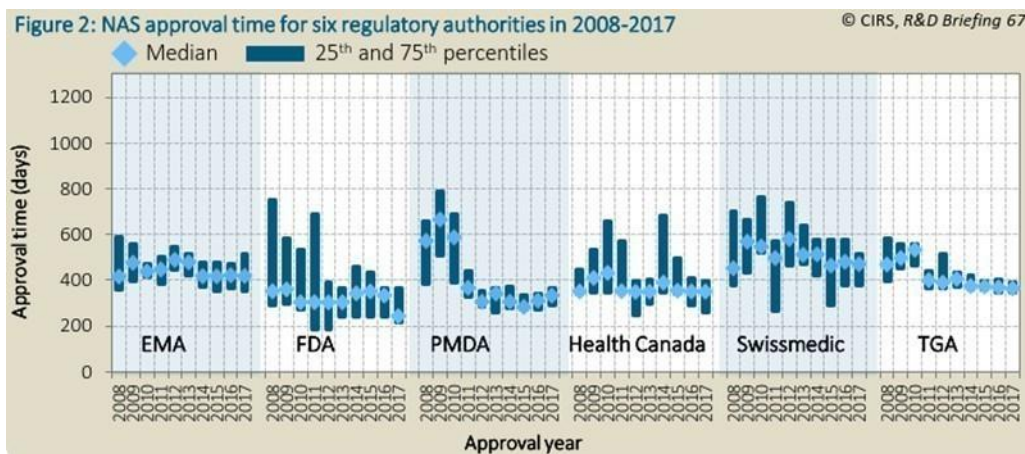
<sup>89</sup> Bujar M, McAuslane N, Liberti L. 2018. R&D Briefing 67: New drug approvals in six major authorities 2008 – 2017: Focus on the availability of medicines and company size. Centre for Innovation in Regulatory Science. London, UK.

<sup>90</sup> As of 2017, TGA does not offer expedited procedures

<sup>91</sup> *ibid.*

Compared to the other agencies in question, the overall fluctuation of approval time seems to be relatively low, especially compared to the FDA, Swissmedic and Health Canada, as indicated by the graph below. This is further supported by the fact that according to Bujar et al. (2018), the decrease in median approval time between 2012 and 2017 years has stemmed almost exclusively from a decrease in company response.

**Figure 58: Comparison of fluctuation**<sup>92</sup>



### 5.3. Do initial marketing procedures support the competitiveness of the European Pharmaceuticals sector?

#### 5.3.1. The ability to choose between different types of marketing authorisation procedures is a competitive advantage for the European market

**The industry's ability to choose between different types of marketing authorisation procedures is a competitive advantage for the European market.**

It allows the industry to adapt its authorisation processes to fulfil its overall marketing strategy. This was confirmed through interviews with industry representatives who indicated that the ability to obtain a marketing authorisation in all Member States or through licence in certain Member States was a flexible approach which was considered as advantageous in comparison to other markets.

The European network encompasses various national legislations, which requires greater coordination efforts. The DCP and MRP address national specificities that do not exist in other, country-sized markets, whilst the CP requiring a Commission decision to ensure legislative coherence across all Member States. The EU system is successful in providing the coordination efforts, thus not impacting the competitiveness of the market. The good predictability and clear timelines of the CP and the flexibility of the MRP/DCP are appreciated by the industry, despite other markets having quicker assessment procedures.

**Despite the US market experiencing stronger support of innovative medicines, new products reach the European market quickly.**

It was highlighted by industry representatives through interview that Europe is lagging in terms of dedicated support to speed up the authorisation innovative medicines, despite the accelerated procedure in place. Through a study undertaken based on industry benchmark data, the FDA in the US approved approximately 60% of all new products via at least one expedited regulatory pathway, with

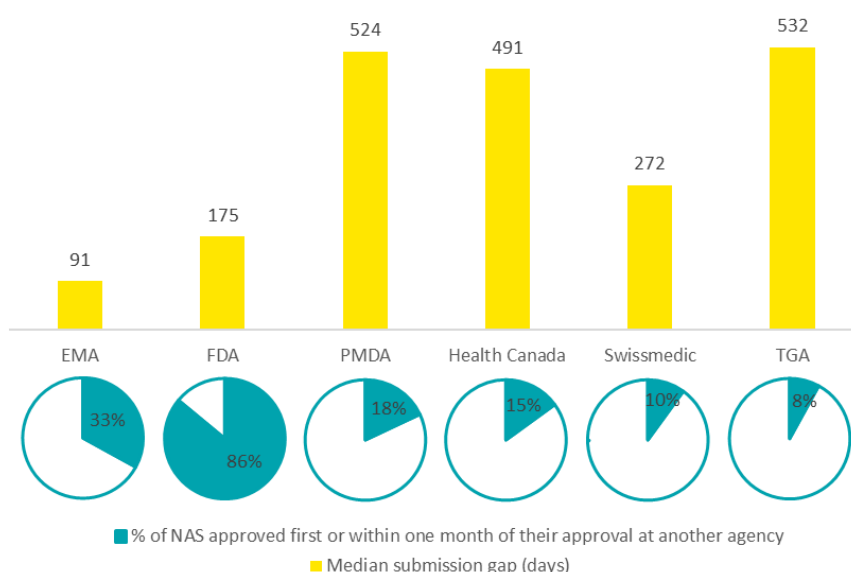
<sup>92</sup> Bujar M, McAuslane N, Liberti L. 2018. R&D Briefing 67: New drug approvals in six major authorities 2008 – 2017: Focus on the availability of medicines and company size. Centre for Innovation in Regulatory Science. London, UK.

Japan approving around 40% of its new products through an expedited approach. In comparison, less than 20% of new products in the EU were approved through an expedited procedure.<sup>93</sup>

One research-based industry umbrella organisation indicated examples of medicines that gain FDA Breakthrough status in the US, but then are not considered to fall under the accelerated procedure in the EU. The difference in status provided to medicines means that in some instances patients in the US have access to medicines earlier than in the EU. The use of facilitated pathways in Europe is used less frequently than in other leading jurisdictions.<sup>94</sup>

Nonetheless, the innovative medicines reach the European market quickly. This is shown by the fact that approval rates of NAS lagged only behind those of the FDA. Specifically, 33% of NAS approved by EMA in 2017 were approved by EMA first or within one month of their first approval by the FDA, PMDA, Health Canada, Swissmedic, or TGA. For those that were approved at a later stage, the median submission gap was 91 days, ranking EMA in first place.

**Figure 59: Comparison of NAS approval and submission gap<sup>95</sup>**



### 5.3.2. The EU continues to be a large market for pharmaceuticals that has grown over the past years

**There has been a continuous increase in the import and export of pharmaceutical products within the EU internal market, with the EU being the largest importer and exporter of medicinal and pharmaceutical products.**

This increase leads to the need to ensure that the internal market is completed in relation to pharmaceutical products to establish a regulatory and legislative framework that favours the competitiveness of the European pharmaceutical sector.

With regard to intra-EU trade, pharmaceutical products represent today 5,3% of total intra-EU trade. This has more than doubled from 156 billion euros to 327 billion euros between 2002 and 2016, with an average growth of 5.4%. Concerning extra-EU trade, in medicinal and pharmaceutical products, this tripled from 76 million euros in 2002 to 220 billion euros in 2016, recording an annual average growth of 7.8%. The figure below shows an overview of the market evolution in the past 15 years.

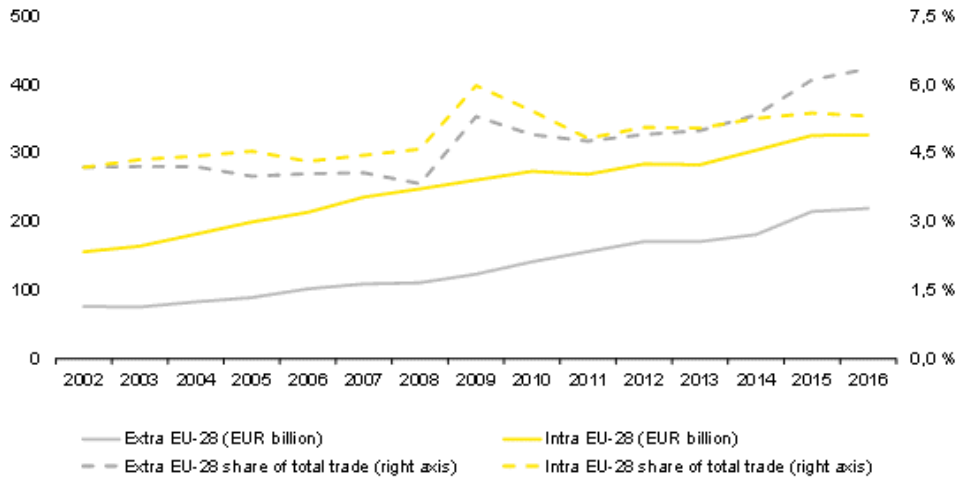
<sup>93</sup> Bujar M, McAuslane N, Liberti L. 2018. R&D Briefing 67: New drug approvals in six major authorities 2008 – 2017: Focus on the availability of medicines and company size. Centre for Innovation in Regulatory Science. London, UK.

<sup>94</sup> *ibid.*

<sup>95</sup> *ibid.*

Amongst the EU Member States, the share of the market is unequally distributed. Belgium (19%), Germany (16%) and the United Kingdom (11%) are amongst the biggest importers. Germany was identified as the largest exporter, accounting for overall a quarter of all extra EU exports in 2016. It was followed by Belgium (13%), the United Kingdom (11%), France and Ireland (10%).

**Figure 60: Extra-EU and intra-EU trade in medicinal and pharmaceutical products (2002-2016)**<sup>96</sup>



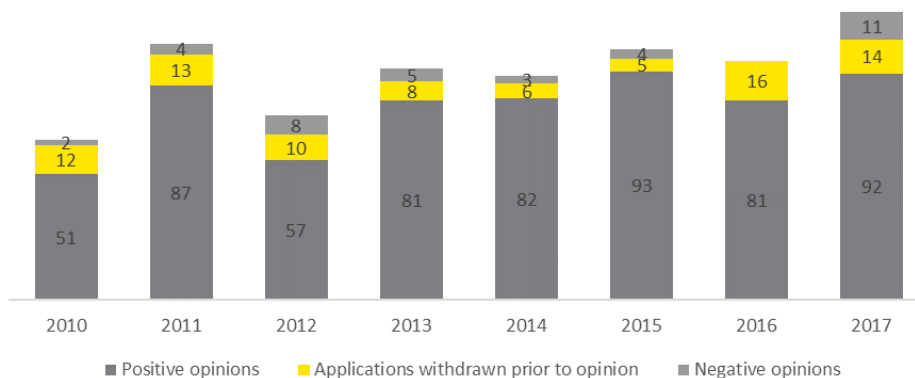
## 5.4. Do initial marketing procedures allow the marketing of reliable products?

### 5.4.1. Appropriate safeguards are in place to ensure the marketing of reliable products

**Appropriate safeguards are in place to ensure the objective of marketing of reliable products.**

The system is sufficiently robust to ensure that product applications are challenged, and further evidence is requested from marketing authorisation applicants before a product is placed on the market. Despite the existence of pre-submission advice, products are regularly not granted marketing authorisation, providing a basic indication that the safeguards of the system are functioning.

**Figure 61: Outcome of initial evaluation applications**<sup>97</sup>



<sup>96</sup> Eurostat

<sup>97</sup> EMA, Annual Reports, 2010-2017

In addition, benefit risk assessment decisions are made available to the public, as European Public Assessment Reports (EPARs) are available following the product authorisation. The assessments are of high quality, as confirmed by industry stakeholders and the product case studies and are adhered to by CHMP and PRAC.

#### **Legislative exceptions are used appropriately.**

All stakeholders agreed that mechanisms such as the accelerated assessment and conditional marketing authorisations are beneficial and provide additional flexibility to the system. As previously mentioned, the overall small numbers of accelerated assessments and conditional marketing authorisation as well as the fact that there have been no negative reactions to these products over the course of the study period point to an overall adequate use of these procedures.

#### 5.4.2. Initial marketing procedures benefit from a high-level of expertise

##### **The system of rapporteurship benefits the marketing authorisation procedure as it ensures an effective assessment of a product.**

The existence of rapporteurs and co-rapporteurs was one of the strengths of the regulatory system as it guarantees a double and full independent assessment for the same medicinal product. It also allows expertise to be built across the system, contributing to the globally unique setting of cooperation between NCAs. This was confirmed through consultation with experts through the online survey, with 98% of experts considering the system of rapporteurship/coordinators in their committees to be effective to a high (57%) or to some extent (41%). 85% of experts considered that the co-rapporteur was assigned to a Member State with the relevant capacity and expertise.

As outlined under Work Package 1 above, there was a shift in the assignment of rapporteurs over the reference period, with multinational teams playing a larger role. The use of multinational teams not only ensures the effective use of expertise from different Member States but also the ability to disperse resources across a number of different NCAs. According to NCAs consulted through the study, the role of the Rapporteurs is clear even in the case of multinational teams. This system is considered as essential to involve NCAs with low capacity / potential to take on a full rapporteurship.

##### **Rapporteur selection procedures could be strengthened.**

The 2010 study concluded that the ‘transparency of rapporteurship appointment procedures should be strengthened’. Whilst certain recommendations relating to ensuring that conflicts of interest of rapporteurs are checked were undertaken, the transparency of rapporteurship appointment could be improved. Though the **role the rapporteur plays in the overall marketing authorisation procedure was not brought into question in the study**, the manner in which these **rapporteurs are designated** was identified as an element where further room for improvement could occur. Rapporteurships are currently allocated by the chairman of the relevant committee, with NCAs expressing their interest in certain dossiers. NCAs indicated during case studies that whilst they have certain preferences in thematic areas, they are not unwilling to lead other dossiers. The choice should be based on objective criteria, namely the ability of the rapporteur to fulfil their role, the competence and expertise of the team and academic expertise of individual assessors. Whilst the overall process seems to be clear, the exact weighting and usage of these criteria is less so. NCAs and experts confirmed this issue through interview, survey responses and Case Studies. Specifically, the consulted NCAs indicated that they would find it useful to provide clear and formal guidance regarding the manner in which rapporteurs are designated. This would not only render the system more transparent but also provide the NCAs with better planning possibilities in anticipation of allocation of resources.

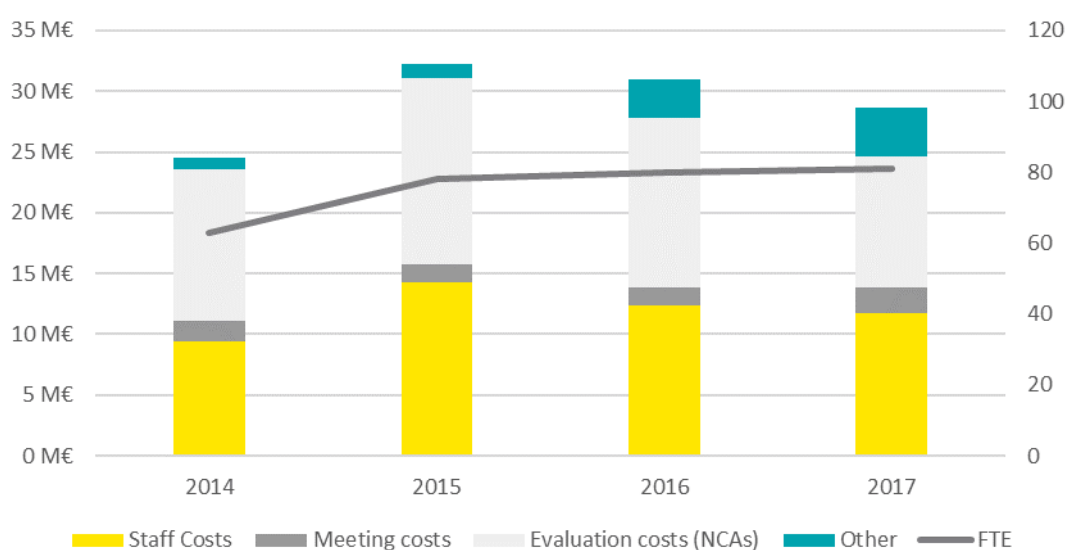


## 5.5. Have initial marketing procedures been successful in ensuring a reasonable level of administrative burden? Are these procedures cost-efficient?

### 5.5.1. The expenditure incurred relating to marketing procedures is proportionate to the overall effectiveness of the procedures

A slight increase has occurred in relation to EMA expenditure, with the highest point reached in 2015 with over 30 million euros.

**Figure 62: Staff and expenditure – Initial Marketing Authorisation (human)<sup>98</sup>**



The costs are proportionate to the overall increase in numbers of products falling under marketing authorisation. The increase from under EUR 25 million expenditure in 2014 to under EUR 30 million expenditure in 2017 is overall representative of advancements made in relation to the applications.

### 5.5.2. The CP has limited administrative burden for the industry, but remains challenging for NCAs

**The centralised procedure is seen as having reduced administrative burden for industry, whilst some burden remains for the NCAs.**

Due to the clear framework and robust procedures in place, the administrative burden on most companies seems to be limited in the centralised procedure regarding initial marketing authorisations. Nonetheless, the complexity of the application for the centralised procedure can present a burden for small companies, who can get too discouraged to proceed. Understanding the necessary requirements entails the need for significant expertise and resources, which may not be available to SMEs. Whilst EMA has created a dedicated support function and put in place and incentives mentioned earlier in the text and whilst national regulatory bodies approach SME's at an early stage to accompany them through early advice, the problem can nonetheless still exist. This was confirmed by EMA which noted that despite applications by SMEs rising over the past year, the proportion of products not receiving authorisation was higher than that of larger companies. However, it needs to be considered that the problem is to an extent inherent, as small companies will always find difficulties in completing complex

<sup>98</sup> EMA, Annual Activity Reports, 2014-2017



applications. This fact should not be a reason to diminish the rigour of the Centralised Procedure, as patient safety remains a key objective.

**As the capacity of the network is already stretched, there is a need for greater flexibility to adapt procedures and deadlines to certain products.**

Currently, the Centralised Procedure applies the same administrative load to all types of procedures. This means that generics require the same process, timelines and documentation as new and innovative products. Similarly, current decision-making procedure at European Commission level for generics is the same as for highly-innovative medicinal products. In light of the increasing workload, considerations could be given as to whether decision making could be simplified for generics, to ensure the system is able to successfully adapt to future challenges and focus on new and innovative products.

**Another potential efficiency gain was identified related to the submission of documentation.**

The marketing authorisation procedure requires a full stand-alone application including all documents without being in a position to refer to already submitted active substance documentation by the same or a different company. A potential was therefore identified to cross-reference to documentation already included in other marketing authorisation applications, as is the case in the US. This would make the centralised procedure more easily accessible for generics and biosimilars, where at the moment, the system implies some administrative burden. These burdens were identified by two NCAs during the case studies and are reflected by the fact that most generic medicines are authorised through either the DCP or MRP.

5.5.3. Diverging views and unharmonised application of the legislation present an administrative burden for industry applicants in the MRP/DCP

**Administrative burden was identified by industry in relation to the DCP and MRP, particularly due to the diverging views that could be provided by Member States.**

For MRP/DCP, burdens can arise due to unharmonised interpretation and application of legislation. This makes procedures less transparent, predictable and efficient for applicants themselves due to inconsistencies across MS.

For example, the current MRP process allows countries to have additional requirements and administrative controls, leading to procedures being delayed in frequent cases. Another example is the case where a CMS may demand that the applicant demonstrates equivalence with other products on its own market, despite a European reference product existing.

For MRP/DCP, burdens can arise in handling procedures where a product is categorised as a prescription drug in one Member State and a non-prescription drug in another. Whilst current legislation in place provides that the legal status of the product is a national issue, the categorisation of the product as prescription/non-prescription impacts the product information which should be provided for that particular product, depending on the Member State in question. Moreover, industry identified difficulties in relation to the risks of mixed legal status throughout the markets in relation to non-prescription medicines which can lead to complexity and administrative burdens for companies wishing to access different markets at EU level. An example was provided by one industry representative regarding OTCs, where Member States allow different claims and require different packaging leaflets. If a company was to apply across all Member States, it would have to adopt the most conservative claims. Hence, different products are developed for different markets, which requires additional processes and presents a potential efficiency gain.

**Product Case Study 8: IBUPROFEN<sup>99</sup>**

Ibuprofen is a painkiller and anti-inflammatory medicine. Ibuprofen is present in medicines as a mixture of two molecules, ibuprofen and dexibuprofen. They are currently available in the European Union (EU) in a number of different formulations. Ibuprofen and dexibuprofen medicines have been authorised in the EU through national procedures and have been available for many years under a wide range of trade names.

<sup>99</sup> The final conclusion of the case study may change depending on additional information to be received.

The medicines are available on prescription and over the counter, depending on the Member State. The exact status by Member State is however not consolidated centrally, making it necessary to inquire with each Member State. This illustrates a case in which differences across Member States pose an administrative burden.

Half of CMDh experts consulted found that diverging approaches among Member States impact procedures. In the open responses, they specified that different national requirements were the main source of inefficiency. This was confirmed by the NCA survey, where 15 out of 22 NCAs agreed that divergences could pose an additional burden to some extent.

In this regard, the implementation of a pilot work-sharing procedure in the assessment of Active Substance Master Files (ASMF) was welcomed by stakeholders of the generics industry as a procedure that eliminates duplication and increases efficiency. In the current system, when an ASMF is used in multiple procedures and/or Member States, it can lead to duplicate assessments and divergent decisions. The work-sharing procedure was implemented by an HMA Working Group and harmonises the assessment and reduces the associated burden. Whilst this procedure is not mandatory, its application is strongly encouraged, as it provides an efficiency gain.

**The industry not adhering to timelines can pose an administrative burden for NCAs.**

As noted by 3 NCAs interviewed during the case studies, there are cases, both regarding the start of the procedure as well as the clock-stop phase, where companies have time to respond to issues raised by the NCAs, where the NCA and the industry agree on a submission date, which in turn is not kept by the industry due to missing documentation or other factors. This leads to planning difficulties on the side of the NCAs, where resources that had been allocated are not used, and once the dossier is submitted, resources are no longer available. This leads to a planning asymmetry where NCAs are required to adhere to strict timelines, but NCAs have no planning certainty to ensure that resources are used optimally to adhere to the set timelines. There have been efforts at NCA and EMA level to set out voluntary best-practices, but so far, they seem to have little effect.

## 6. Work Package 4: Post-Marketing Authorisation Procedures

The aim of this Work Package is to examine the extent to which post-marketing authorisation procedures effectively and efficiently contributed to improve the level of health protection of EEA citizens.

In detail, this section aims to answer three questions:

1. To what extent are post-marketing authorisation procedures effectively applied and mutually complementary?
2. Do post-marketing authorisation procedures contribute to a higher degree of health protection for EEA citizens?
3. To what extent are post-marketing authorisation procedures efficient? Do they avoid any unnecessary administrative burden?

### Synthesis

Pharmacovigilance activities, referrals, and variations provide a **solid framework for post-marketing authorisation activities** to achieve the objective of strong market surveillance and monitoring:

- ▶ ADR reporting mechanisms have been expanded continuously, especially regarding patient involvement, with patient submitted ADRs rising from 19,184 in 2011 to 90,385 in 2017
- ▶ The review procedure of ADRs allows the identification of potential risks and give EMA and NCAs the possibility to take necessary regulatory steps. Around 2,000 signals are detected each year, leading to around 100 validated signals each year.

The identification of risks could be further improved by integrating real world data into the procedures, an undertaking that would require building expertise on big data and statistics.

**The administrative burden** on Variations and Risk Management Plans can be reduced.

- ▶ Variations, although effective, come with significant administrative burden. The high number of Type IA variations (around 3,000 per year) mean a simplified system would present significant efficiency gains.
- ▶ Full Risk Management Plans for generics do not seem to be necessary, as the active substances have been known for a long time and the full safety profiles are detailed in the pharmacopeia, making all relevant information readily available.

The new pharmacovigilance legislation has **increased the robustness of post-authorisation activities** in general. Notably the creation of PRAC in 2012 has provided a more formalised setting for pharmacovigilance activities, taking a coordinating role between the various tools such as Risk Management Plans (RMP), the Periodic Safety Update Reports (PSUR) and the Post-Authorisation Safety Studies (PASS).

This puts into question the relevance of renewals. With strong monitoring activities in place, a formalised review of the authorisation after 5 years no longer seems necessary.

The greater coordination efforts have also led to a constant decrease in referrals, with the diminishing frequency outweighing the complexity of the procedure.

Beyond the monitoring of authorised medicines, **EU coordination mechanisms to respond to health threats are working well**, as evidenced by the H1N1 outbreak. However, the area of medicine shortages remains a risk, as EU coordination mechanisms are not yet formalised and data availability is generally low.

### 6.1.1. The existing post-marketing authorisation procedures provide an extensive system of monitoring and surveillance

The study examined the overall suitability of the post-marketing authorisation procedures, focusing on the four major components:

- ▶ Pharmacovigilance procedures
- ▶ Referrals
- ▶ Variations
- ▶ Renewals

The context and legislation related to these categories can be found in Section 2.

#### **The implementation of the new legislation has formalised the framework for pharmacovigilance activities and enhanced cooperation, notably through the creation of PRAC.**

Pharmacovigilance procedures have undergone a significant evolution over the past years, triggered by the revision of the pharmacovigilance legislation through modification of the Directive 2001/83/EC, through Directive 2010/84/EU and Regulation (EU) No 1235/2010, accompanied by Commission Implementing Regulation No 520/2012, which came into effect in 2012.<sup>100</sup> In short, the legislation had two distinct aims:

- ▶ **To reduce the number of ADRs<sup>101</sup>** through the collection of better data on medicines and their safety, rapid and robust assessment of issues related to the safety of medicines, effective regulatory action to deliver safe and effective use of medicines, empowerment of patients through reporting and participation, increased levels of transparency and better communication.
- ▶ **To improve the post-marketing authorisation procedures for applicants and holders** through making their roles and responsibilities clear, minimising duplication of efforts, freeing up resources by rationalising and simplifying reporting on safety issues, establishing a clear legal framework for post-authorisation monitoring.

#### **The changes in the pharmacovigilance legislation have strengthened overall pharmacovigilance activities of the system.**

This was evidenced by a study by Arlett et al. (2014)<sup>102</sup>, which noted that the implementation of the legislation is demonstrating results in terms of patient safety and the availability of effective and reliable drugs. It found that process indicators such as RMPs, ADRs, signals, PSURs and EU Pharmacovigilance Referrals point to more systematic and proportionate risk management planning, an increase in reporting, improved coordination of signal management, and faster assessment and decision making in pharmacovigilance procedures. As of today, 90% of experts are satisfied with the pharmacovigilance system in place. Those that did not agree pointed out the extensive reporting requirements for generics (discussed in more detail in sub-section 6.3.2) as well as differences between MS for non-centralised procedures. NCAs offered a similar view, with 19 out of 21 showing satisfaction with the pharmacovigilance mechanisms in place. The two that disagreed mentioned that pharmacovigilance procedures could be more stringent, as a number of procedures are not binding and that the Eudravigilance database was not performing in line with expectations.

#### **The creation of the Pharmacovigilance Risk Assessment Committee (PRAC) in 2012 was an essential part of the new legislation.**

PRAC is responsible for assessing and monitoring the safety of human medicines. It has directly contributed to establishing a clear framework for post-authorisation monitoring. Whilst interviewed stakeholders from pharmaceutical industry and NCAs pointed out that the role of PRAC and its alignment with other Committees was not immediately clear, the system evolved to become clear and

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<sup>100</sup> A more detailed description of this legislation can be found in Chapter 2

<sup>101</sup> See section 6.2.2 for more information

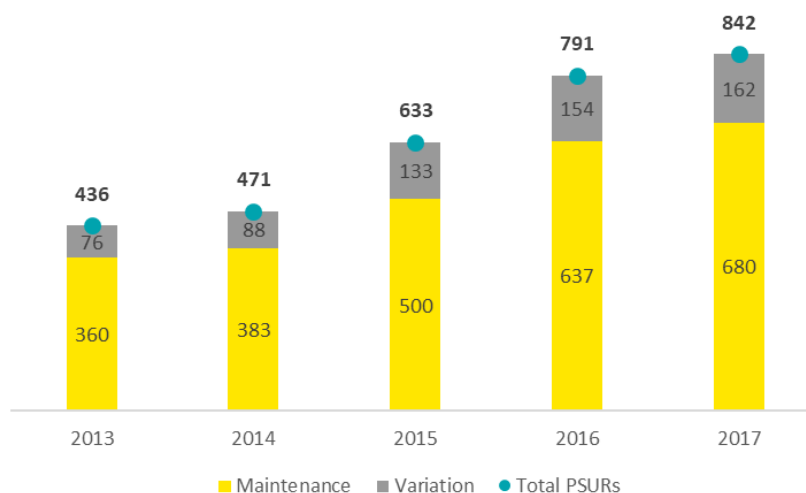
<sup>102</sup> Arlett, P., Portier, G., De Lisa, R., Blake, K., Wathion, N., Dogne, J. M., Spooner, A., Raine, J., & Rasi, G. (2014). Proactively managing the risk of marketed drugs: experience with the EMA Pharmacovigilance Risk Assessment Committee. *Nature reviews Drug discovery*, 13(5), 395.

effective. Regarding the cooperation with other working parties, 83% of non-PRAC experts were satisfied overall with the communication between their Committee/Working Party and PRAC. 75% of PRAC members outlined their satisfaction with the communication with other Committees/Working Parties.

After its creation, PRAC has taken a coordinating role and been involved with key existing and new aspects of pharmacovigilance, namely the **Risk Management Plans (RMP)**, the **Periodic Safety Update Reports (PSUR)** and the **Post-Authorisation Safety Studies (PASS)**. Each of these mechanisms present reporting requirements on the safety of a medicine. Whilst the RMPs need to be submitted during the initial marketing authorisation procedure and updated throughout the life cycle of the product, PSURs and PASS are only necessary once the marketing authorisation has been granted.

PSURs have to be submitted by marketing authorisation holders to the regulatory authorities at predefined intervals. They summarise data on benefits and risks of a medicine, taking into account all studies that were carried out on this subject. PSURs can be submitted to a **single product** or for **multiple products** with the same active substance. The latter option, which is known as PSUR single assessment procedures (PSUSAs), was newly introduced with the pharmacovigilance legislation. PSURs are subsequently assessed by the regulatory authorities and can entail changes to the product information. The number of PSURs has constantly increased over the past years, reaching 842 in 2017. The percentage of PSURs that lead to a variation has remained constant around 20%. This means that whilst reporting on risks has increased, the proportion of cases that require a modification of the marketing authorisation has stayed constant.

**Figure 63: Evolution of PSURs<sup>103</sup>**



### Product Case Study 9: ELAPRASE

The product was designated as an orphan medicine on 11 December 2001 and received marketing authorisation in January 2007. Elaprasedipine was withdrawn from the Community register of orphan medicinal products in January 2017 at the end of the 10-year period of market exclusivity.

The product was under additional monitoring as it was authorised under exceptional circumstances. Specific obligations have been imposed on the market authorisation holder and are periodically reviewed to assess the benefits/risks balance. In addition, the PRAC is involved for each Periodic Safety EU Single Assessment. There were annual reassessments of the products, in which the CHMP concluded the MA should be maintained.

The process shows the successful application of the monitoring processes of products in the post-authorisation process, contributing to the safety of products on the market.

A final part of post-authorisation procedures is the **sunset clause**. The clause is a legal provision stating that the marketing authorisation of a medicine will cease to be valid if the medicine is not placed on the

<sup>103</sup> EMA, Annual Reports 2010-2017

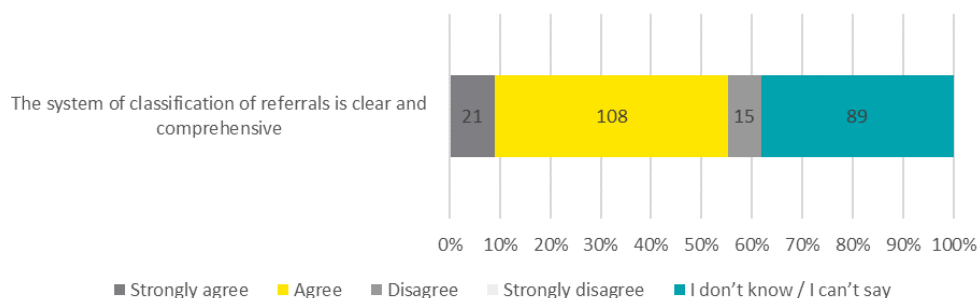
market within three years of the authorisation being granted or if the medicine is removed from the market for three consecutive years. This is to ensure marketing authorisations remain relevant. However, the relevance of the sunset clause was questioned in interviews with both industry and NCAs. Stakeholders noted that the clause does not seem to be applied since companies take the natural decision on whether to maintain their marketing authorisation without the influence of a sunset clause.

**The complexity of referrals is outweighed by the fact that they have been diminishing over the past years due to closer coordination efforts.**

The legislative framework provides a clear distinction between the different types of referrals, distinguishing between safety related referrals and referrals regarding harmonisation of DCP/MRP procedures.

**For the centralised procedure**, 89% of experts considered the system of classification of referrals to be clear and comprehensive. The effectiveness of referrals is confirmed by NCAs, with 18 out of 20 finding it to be clear and comprehensive (2 could not respond to the question).

**Figure 64: With regard to the centrally authorised procedures, to what extent do you agree with the following statements?**

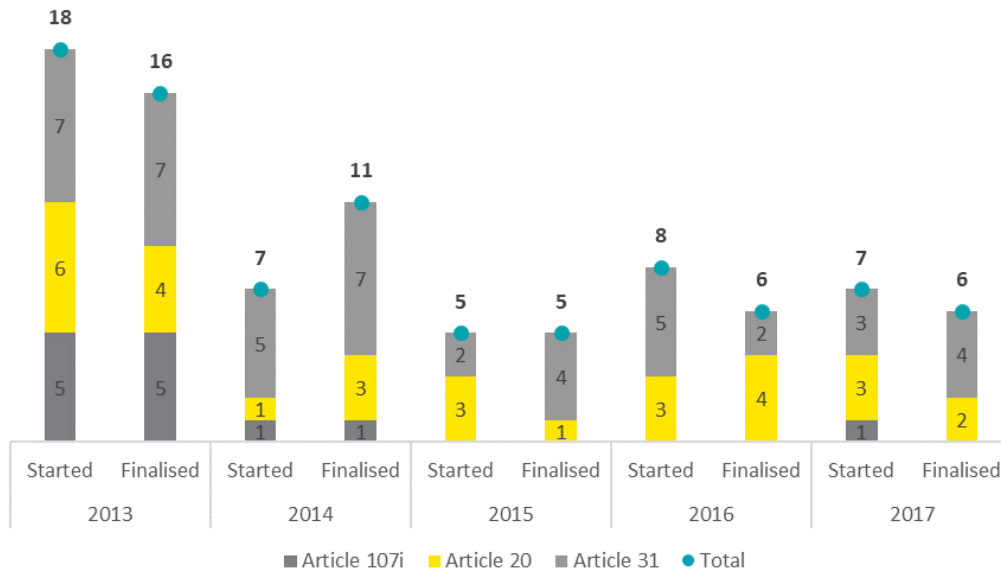


Source: Expert Survey

EMA as well as around 5 experts mentioned that the **procedure in place for referrals can be burdensome and complex**. However, a significant decrease has been observed in pharmacovigilance related referrals over the past years, from 18 procedures started in 2013 to 7 procedures started in 2017. This points to an increased harmonisation across EEA Member States, which may be due to the fact that PRAC provides a formalised setting for cooperation between MS in the area of pharmacovigilance, an argument confirmed by Arlett et al. (2014).<sup>104</sup> This interpretation is also offered by the generics industry, which cites opportunities for dialogue as a reason for the progressive reduction of referrals necessary over time. This means that **if safety issues are effectively addressed at an earlier stage of the procedure, the need for referrals diminishes**. It is noteworthy that the number of urgent safety referrals, as provided in Article 107i, which can entail the suspension or revocation of a marketing authorisation or the prohibition of the supply of a medicine, has gone towards zero over the past years.

<sup>104</sup> Arlett, P., Portier, G., De Lisa, R., Blake, K., Wathion, N., Dogne, J. M., Spooner, A., Raine, J., & Rasi, G. (2014). Proactively managing the risk of marketed drugs: experience with the EMA Pharmacovigilance Risk Assessment Committee. *Nature reviews Drug discovery*, 13(5), 395.

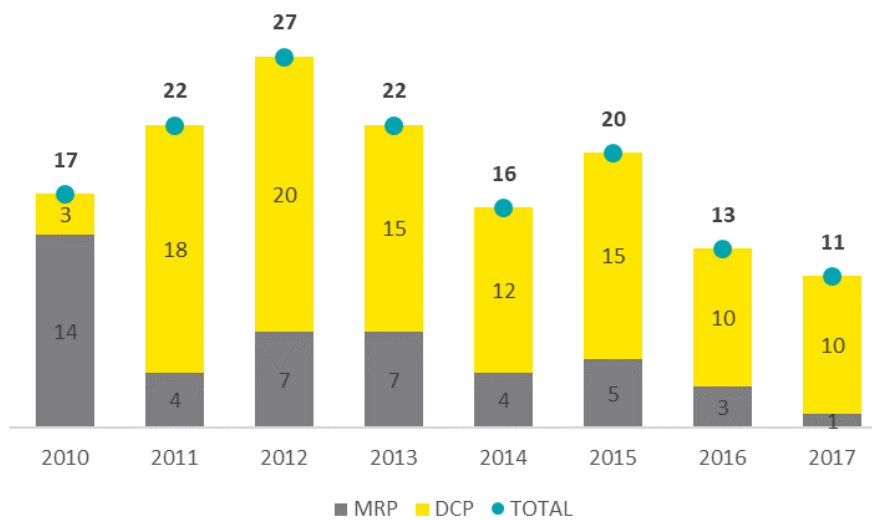
**Figure 65: Arbitrations and referrals by legal basis<sup>105</sup>**



Looking at the outcomes of pharmacovigilance related referrals, the most prominent outcome is a change in product information. In 2017, of the completed procedures, four referrals led to changes in product information of which one led to the suspension of the marketing authorisation and one led to both changes in product information for some medicines and the suspension of the marketing authorisation for others. In 2016, five referrals led to changes in product information whilst one led to a revocation of the marketing authorisation.

**Concerning CMDh referrals**, the number of referrals also decreased over the study period. With the exception of 2010, the majority of CMDh referrals were related to products falling under the DCP. Similar to referrals under the CP, the overall number of products referred to the CMDh is decreasing. The decrease is apparent to industry stakeholders as well, which note that the number of referrals needed for the DCP, especially in the area of generics, has reduced over time through dialogue, cooperation and harmonisation.

**Figure 66: Procedures referred to CMDh per type of procedure<sup>106</sup>**



<sup>105</sup> EMA, Annual Report 2017

<sup>106</sup> HMA, Annual Statistics 2010-2018



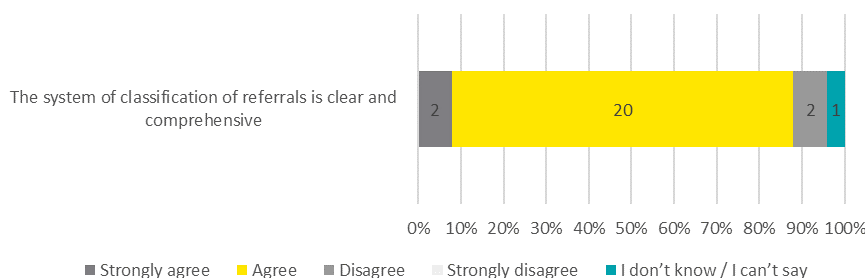
### Product Case Study 10: QUINOLONE<sup>107</sup>

Quinolones are a class of antibiotics which are widely prescribed in the European Union and are important for treating serious, life threatening bacterial infections. The EMA reviewed these medicines due to reports of serious persistent side effects mainly affecting muscles, joints and the nervous system

The review of fluoroquinolones and quinolones was initiated on 9 February 2017 at the request of the German medicines authority (BfArM), under Article 31 of Directive 2001/83/EC. PRAC subsequently recommended restricting the use of fluoroquinolone and quinolone antibiotics (used by mouth, injection or inhalation) following a review of disabling and potentially long-lasting side effects reported with these medicines. A decision was taken in March of 2019.

Whilst the substance has been used since 1961, it has repeatedly been subject to referrals due to long-term side effects that were only discovered through long-term surveillance. This case study shows that referrals are working to address safety concerns, despite the length of the procedure, and does so successfully also for established substances.

**Figure 67: With regard to products authorised through the decentralised and mutual recognition procedures, to what extent do you agree with the following statements**



Source: Expert Survey (CMDh experts only)

Whilst EMA and some experts have noted the complexity of the procedure, the fact that the overall number of referrals is progressively decreasing both for CP and MRP/DCP as well as the fact that the large majority of experts and NCAs found the procedure to be clear and comprehensive leads to the conclusion that referrals contribute to the effectiveness of post-authorisation activities in their current form.

**Variations are a necessary procedure; however, they continue to represent significant administrative burden.**

Classification and conditions under which requests for variations are submitted are laid down in Commission Regulation (EU) No 1234/2008 with a distinction between variations for the CP and DCP/MRP. The legislation became applicable in 2010 with the intention to make the legal framework for variations simpler, clearer, and more flexible as well as to reduce the overall administrative burden of the procedure. The reform was not as effective as it had been hoped, and notable administrative burdens persist. These are discussed in detail in section 6.3, which looks at the efficiency of post-authorisation procedures.

Despite the criticisms, variations successfully address a need in the system to ensure information related to products with a marketing authorisation is correct and up to date. Despite the administrative burden, the procedure is important and does not provide any duplications with other procedures.

**The distinction between the different types of variations is clear in most cases, as there is sufficient clarification in the legal texts as well as in accompanying documentation.**

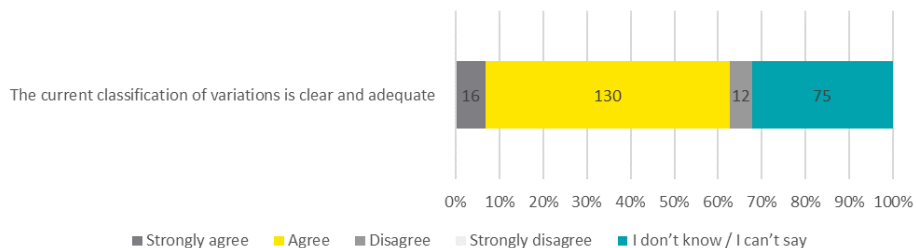
The distinction between the different types of variations is generally clear. However, at times, for the MRP/DCP there can be differences of interpretation between Member States, as confirmed by industry representatives. Instead of accepting the type of variation indicated by one Member State, some

<sup>107</sup> The final conclusion of the case study may change depending on additional information to be received.

Member States prefer to complete their own assessment and procedure. This leads to a duplication of efforts and in the cases where two different conclusions are reached, additional burden for the MAH.

NCA's also generally supported the system, with around 80% (18 out of 22) of NCA's agreeing that the system is clear and adequate for products authorised through all three procedures. Those who disagreed pointed out that the classification of variations is too detailed between Type IA and Type IB variations. Furthermore, they mentioned a need to update variations, especially related to article 5 procedures.

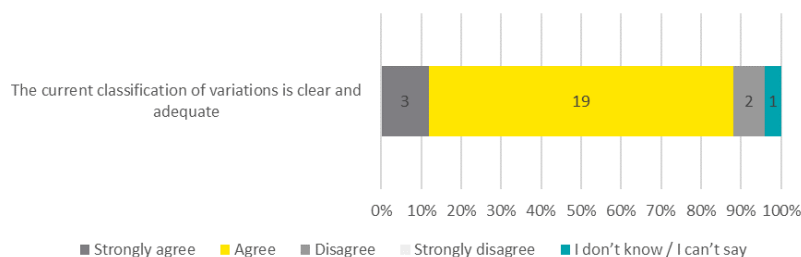
**Figure 68: With regard to the centrally authorised procedures, to what extent do you agree with the following statements?**



Source: Expert Survey

Regarding products authorised through the MRP/DCP procedures, the numbers increased with 88% of CMDh experts agreeing that the current classification of variations is clear and adequate.

**Figure 69: With regard to products authorised through the decentralised and mutual recognition procedures, to what extent do you agree with the following statements**



Source: Expert Survey (CMDh experts only)

**Looking at the timelines of variations, there seem to be differences according to the procedure.**

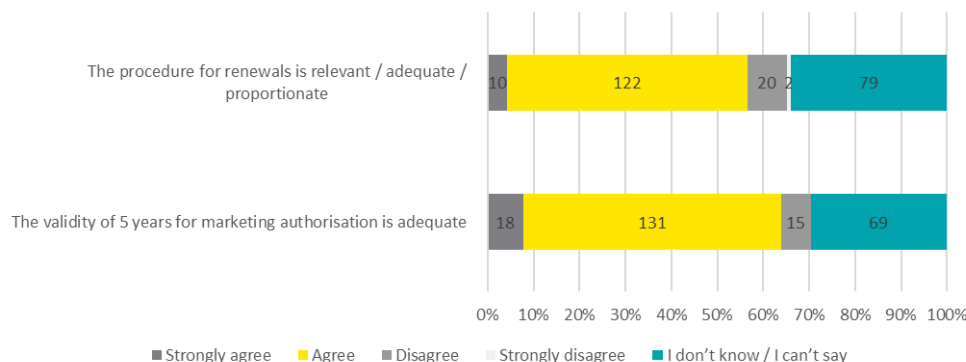
EMA reports that the average assessment time for Type II variations that include an extension of indication is in line with the 90 Day timetable set forth by the legislation. Looking at the shorter timetables, the generics pharmaceutical industry reports less adherence to timelines for the MRP/DCP. For a sample of Type IB variations, the majority of procedures start within 30 days of the foreseen timeline. However, less than 20% start within 15 days, with 3% starting later than 6 months after the submission. More extreme differences can be found regarding variations following safety referrals, where the start date can range between 10 days and 118 days after submission, and the closure of the procedure taking up to several months. This provides uncertainty to the industry. At the same time 2 NCA's interviewed during the case studies pointed out that Type II variations often amount to the same workload as a new procedure. This means that the corresponding amount of resources needs to be mobilised, likely increasing the length of the procedure. Currently, NCA's have little visibility of when a Type II variation comes in, which presents a resource planning issue making it difficult to adhere to strict timelines.

**The effectiveness and complementarity of renewals is questioned.**

In theory the requirement to renew the marketing authorisation of a product five years after its initial application presents an opportunity for the regulatory bodies to re-examine any potential safety concerns.

85% of experts were of the view that the procedure is relevant, adequate and proportionate concerning the validity period for marketing authorisation, and 90% considered the validity period for the marketing authorisation to be adequate. This indicates a general agreement of experts with the renewal procedures in place.

**Figure 70: With regard to the centrally authorised procedures, to what extent do you agree with the following statements?**



Source: Expert Survey

However, the overall effectiveness and complementarity of renewals can be questioned. Due to the large number of post-marketing authorisation activities, such as RMPs, PSURs, PASS, variations, and referrals, **the overall added value of a mandatory review of a marketing authorisation after 5 years is limited**. This is especially the case for medicines with a well-known active substance and an established safety profile. A full evaluation of these products after 5 years seems like an unnecessary step, as products with identical characteristics have been on the market for a long time. Any issues that may exist would have been noticed at an earlier stage. This is explicitly mentioned by two NCAs as well as supported by around 20 experts, which note that ‘the renewal procedure seems to be unnecessary’.

The case against the relevance of renewals can also be made for products with lesser known active substances. As every PSUR review in the current system contains a benefit/risk evaluation, the necessity of a formalised re-evaluation after five years can be questioned. The renewal procedure is not likely to identify issues that have not been discovered through signal detection or PSURs at an earlier stage. The superfluous nature of renewals is further underlined by the fact that the **process has been abolished with the new legislation on veterinary medicinal products**.<sup>108</sup>

## 6.2. Do post-marketing authorisation procedures contribute to a higher degree of health protection for EU citizens?

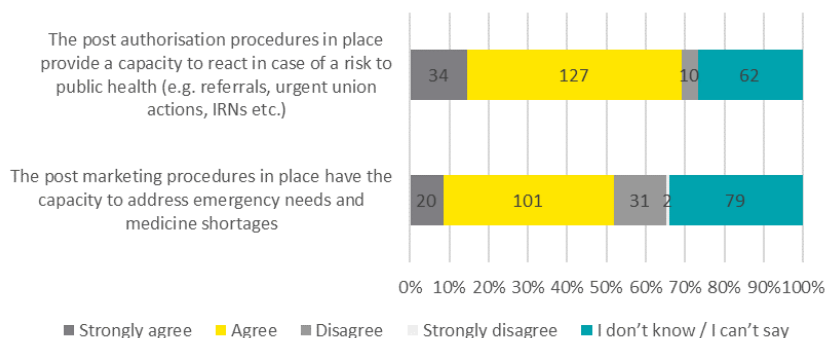
### 6.2.1. The post-authorisation procedures have the capacity to react in case of risk to public health, but medicine shortages can be a challenge

**Post-authorisation procedures in place provide a capacity to react in case of a risk to public health.**

The good reactivity of the system to adapt to health crisis was shown during the H1N1 outbreak, where the CHMP and PRAC engaged rapidly and played a crucial role in the joint efforts against the disease. The observed reactivity of the system was confirmed by 94% of expert respondents who considered post-authorisation activities had the capacity to react to public health risks for the centralised procedure, and 86% found the same for national procedures.

<sup>108</sup> Regulation (EU) 2019/6

**Figure 71: With regard to centrally authorised products, to what extent do you agree with the following statements?**

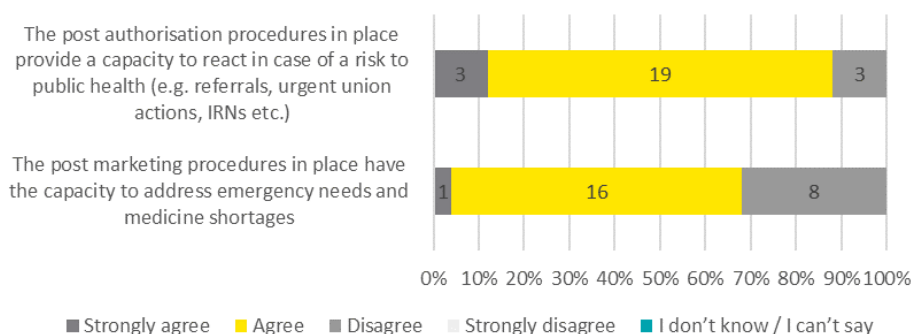


Source: Expert Survey

**Post-authorisation procedures are less well adapted to react to medicine shortages due to little harmonisation and a lack of data.**

Concerning the capacity to address emergency needs and medicine shortages, only 51% of experts considered that post-marketing authorisation procedures within the centralised procedure had such capacity, with 66% agreeing for national procedures.

**Figure 72: With regard to the products authorised through decentralised and mutual recognition procedure, to what extent do you agree with the following statements?**



Source: Expert Survey

Experts that disagreed regarding the capacity to address emergency needs through both the CP and DCP/MRP mentioned that especially if only one manufacturing site of an active substance exists, in case of an issue on that site, it would be difficult to address emergency needs. These experts also noted that **the lack of EU legislation on addressing emergency needs such as medicine shortages as well as the cumbersome coordination approaches both between Member States as well as committees do not allow the system to act fast and flexible.** A last issue identified was the lack of overall understanding of the issue, as there is **little quantifiable data on potential scale, causes and duration of shortages.** In light of this, there is a need to fully examine the issue through market research and studies.

Subsequently, potential was identified for more mechanisms to be put in place at European level, to ensure the system is well prepared and capable to react quickly. It should be noted that, whilst outside of the scope of the study, an EMA/HMA task force on the availability of medicines has been created and a recent pilot has been launched of a system of a single point of contact (SPOC) at NCA and EMA level.

6.2.2. The system has extensive safety monitoring mechanisms in place

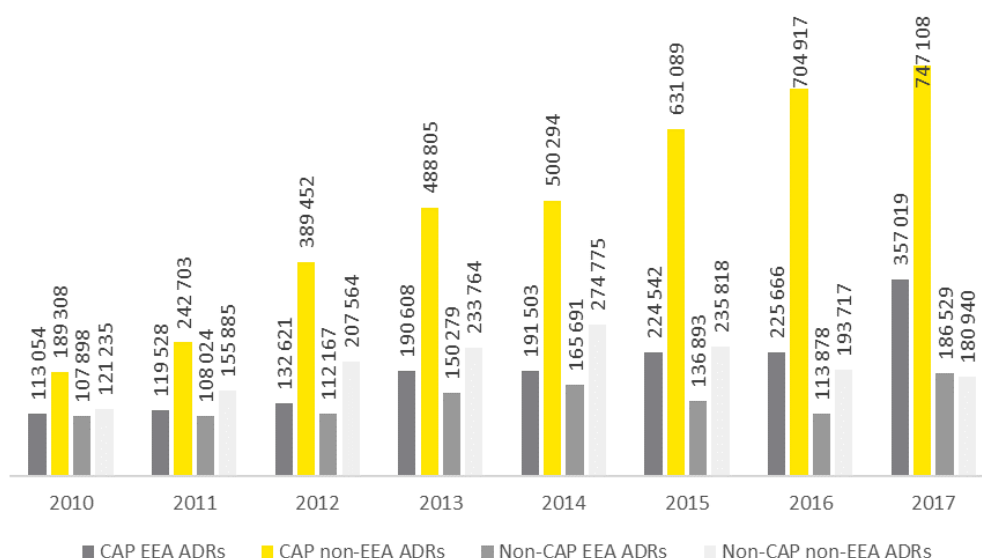
**The implementation of a new Eudravigilance system has led to an increase in the collection of ADRs and allowed for better reporting mechanisms.**

Both EMA and NCAs are required to monitor adverse drug reaction (ADR) data. ADRs are collected through the Eudravigilance system, an electronic system specifically designed to collect and monitor ADRs.

The number of ADRs reported has increased significantly over the study period. This is driven by a fourfold increase of ADRs submitted from non-EEA countries and related to centrally authorised products as well as a threefold increase in ADRs submitted from EEA countries and related to centrally authorised products.

The increase, whilst standing in contrast to the goal of the revised pharmacovigilance legislation, does not mean that adverse reactions have increased, but rather that reporting and collection mechanisms have improved. This is supported by the fact that there has been a twofold increase of ADR reports submitted by patients between 2016 and 2017, which coincides with the introduction of a new Eudravigilance system which increased the scope of mandatory reporting to non-serious cases. In general, there is a positive trend in patient reporting, which can be traced back to increased communication and awareness efforts by EMA and NCAs.

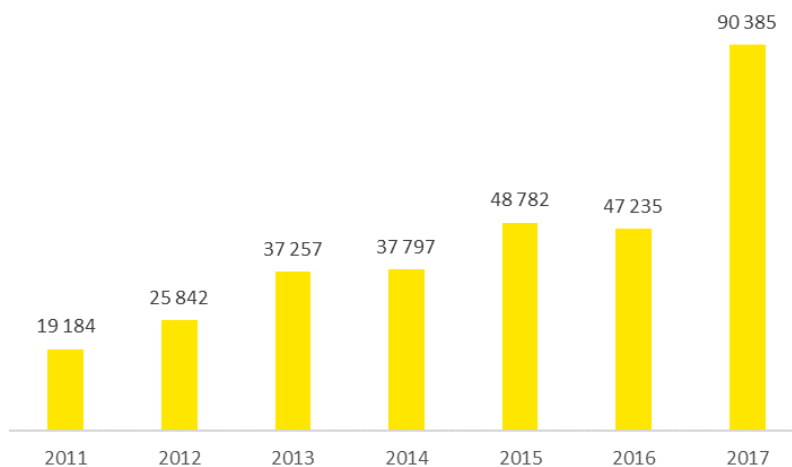
**Figure 73: ADR reporting<sup>109</sup>**



ADRs are reported in the Eudravigilance system by MAH, clinical trial sponsors and NCAs. Reports from patients and consumers are addressed to NCAs, which subsequently report them. One form of ADR reporting concerns the monitoring of medical literature. Prior to September 2015, this was the responsibility of the MAH. This process however led to duplications, as MAH would file multiple reports for the same active substance included in more than one medicine. To counteract this, since September 2015, EMA is responsible for the monitoring of medical literature for the centralised procedure and the entry of the relevant data into Eudravigilance. This has increased both effectiveness and efficiency of the system; as data quality was improved and a source of duplications was eliminated.

<sup>109</sup> EMA, Annual Reports 2010-2017

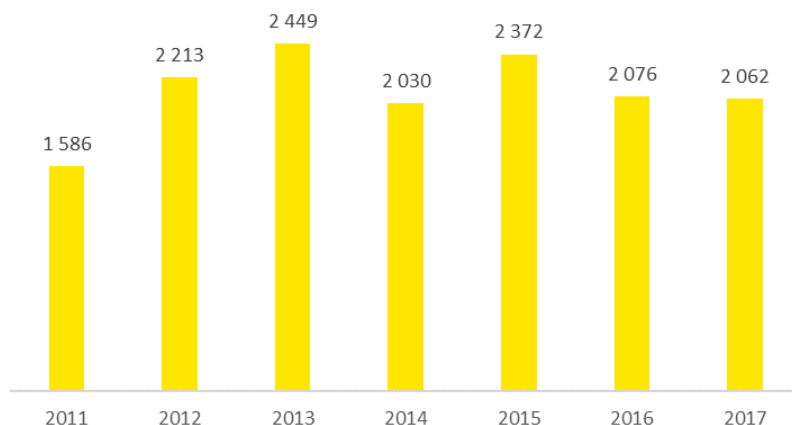
**Figure 74: ADR reports submitted by patients<sup>110</sup>**



**The review of ADRs and subsequent signal detection process is working well both on EU and national level.**

Following their submission to the Eudravigilance system, ADRs are then reviewed together with other sources such as clinical studies and scientific literature to generate safety signals. The evaluation of these safety signals is part of general pharmacovigilance activities, to verify whether there is a clear link between a substance and the adverse reactions. If a link is confirmed, regulatory action would be necessary. The number of signals detected over the study period has fluctuated around 2,000 signals per year.

**Figure 75: Signals detected<sup>111</sup>**

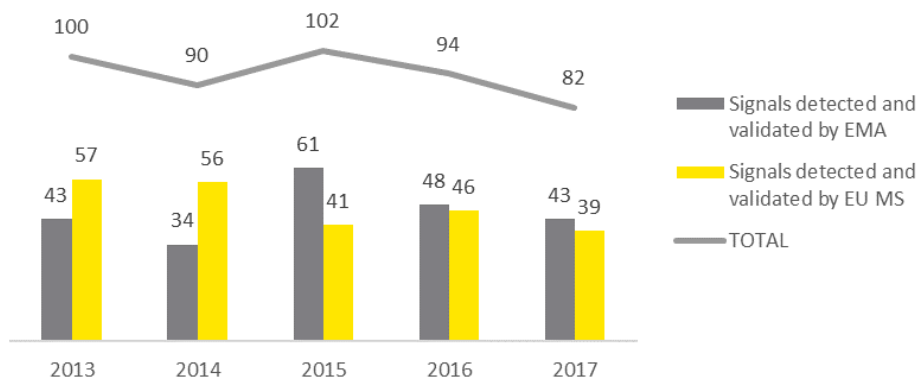


All signals detected are assessed by the regulatory authorities. Those where a clear link between an adverse effect and a substance is shown are validated by either EMA or the NCAs. The number of validated signals has slightly decreased over the study period, from 100 in 2013 to 82 in 2017. It is interesting to note that whilst initially the majority of signals were detected and validated by the Member States (57 v 43 in 2013), but this was no longer the case in recent years (43 by EMA v 39 in 2017).

<sup>110</sup> EMA, Annual Reports 2011-2017

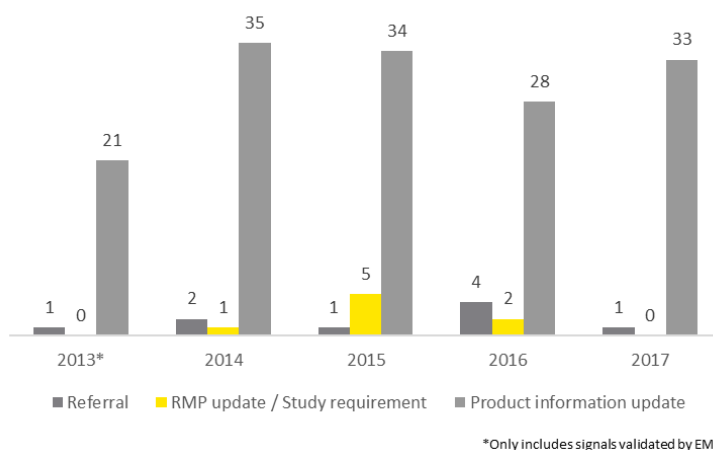
<sup>111</sup> EMA, Annual Reports 2011-2017

**Figure 76: Outcome of signal assessment<sup>112</sup>**



The largest parts of validate signals lead to a change in the product information. Per year, only a few signals lead to regulatory action, such as a referral, an update of the RMP or the requirement to conduct a study. The graph below presents the outcomes of signal assessment per year, not including those that did not require further steps and those that were not finalised within the year they were validate.

**Figure 77: Outcome of validated signals<sup>113</sup>**



### 6.2.3. Incorporation of real-world data should be considered

**There is an increased need to incorporate real-world data more actively into monitoring of medicines post-authorisation was highlighted, recognised by EMA and various MS.**

Whilst EMA is currently putting effort into developing this field, funding in the area is limited and there is no explicit legal basis or formalised mechanism for its incorporation. This stands in contrast with other markets such as the US, where there has been a significant investment to ensure real world data is taken into account when making decisions. The EMA system currently still relies heavily on clinical trials regarding post-authorisation activities, as there is a lack of funding as well as capacity and expertise to integrate real world studies. This will need to be developed alongside the digitalisation of health data and the increase of statistical and big data expertise within the Agency (see section 3.3.1). The FDA has already launched an initiative to increase its capability to make use of big data and real-world evidence by expanding its Sentinel System<sup>114</sup> by adding additional data sources and linkages as well as improving algorithms and data-mining capabilities.

<sup>112</sup> EMA, Annual Reports 2013-2017

<sup>113</sup> EMA, Annual Reports 2013-2017

<sup>114</sup> The Sentinel Initiative is a long-term effort to improve the FDA's ability to identify and assess medicinal product safety issues through surveilling electronic healthcare data.



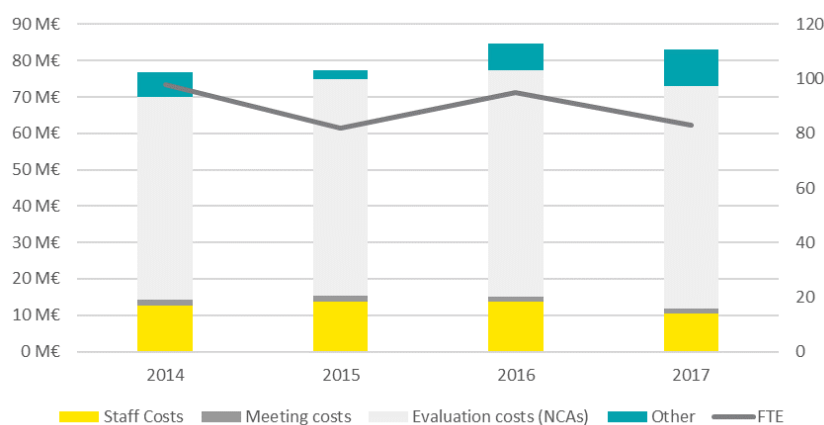
## 6.3. To what extent are post-marketing authorisation procedures efficient? Do they avoid any unnecessary administrative burden?

### 6.3.1. Expenditure related to post-marketing authorisation activities has evolved with the level of work

**The costs related to post-marketing authorisation procedures for human medicines have remained relatively constant over the past 4 years.**

They amounted to EUR 76,8 million in 2013 and EUR 82,9 million in 2017, with a slight decrease in the number of FTE from 98 in 2013 to 82 in 2017. The relative stability can be compared to the relatively constant number of variations and renewals over the past years.

**Figure 78: Staff and expenditure – Post-Marketing Authorisation (human) <sup>115</sup>**

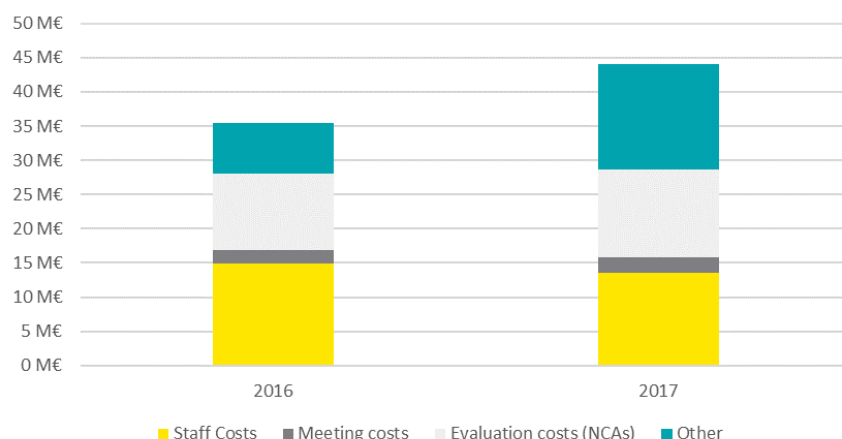


**When looking at pharmacovigilance activities, there has been a significant increase in expenditure since the previous study.**

Expenses have tripled, from EUR 22 million in 2008 to EUR 44,1 million in 2017. This is in one part due to the evolution of the pharmacovigilance legislation and notably the creation of PRAC. Between 2016 and 2017, a jump in expenditure can be observed, driven by costs related to IT due to the implementation of the new IT systems such as the Eudravigilance system.

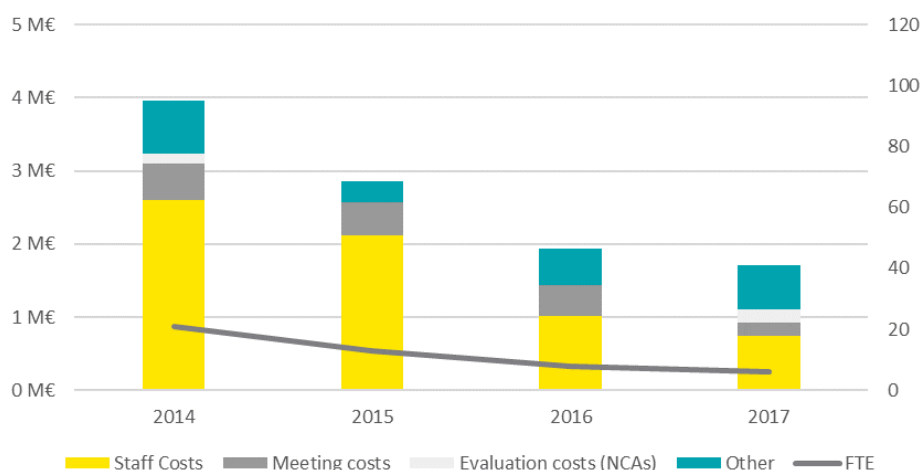
<sup>115</sup> EMA, Annual Activity Reports 2013-2017

**Figure 79: Expenditure – Pharmacovigilance (human)**<sup>116</sup>



Whilst the expenditure in pharmacovigilance has increased, that related to referrals has decreased by more than 50%. At the same time, FTEs on this matter have also decreased. This is in line with the general decrease of referrals previously identified, showing an efficient system adapting to the workload.

**Figure 80: Staff and expenditure – Referrals (human)**<sup>117</sup>



### 6.3.2. There are potential efficiency gains regarding administrative requirements

#### **Efficiency gains are possible related to administrative burden and reporting requirements.**

A potential for time-saving exists in relation to post-marketing authorisation procedures. Efficiency gains were identified in three main areas, renewals, Risk Management Plans, and variations. This was confirmed by 60% of experts responding to the online survey who were of the view that no time savings could be made.

**Firstly, as previously mentioned, the relevance of renewals can be questioned.** As post-authorisation activities, especially pharmacovigilance activities already aim to closely follow the development of a medicine once it is on the market, renewals could be seen as a duplication of efforts. In this case, efficiency could be increased if resources allocated to renewals were used otherwise.

A second potential efficiency gain concerns **Risk Management Plans (RMPs)**. Currently, every medicine going through the authorisation procedure needs to submit an RMP along with its application. The RMP includes information on the medicines safety profile, how risks will be minimised and plans for studies or other activities to learn more about the safety of the product. According to the current

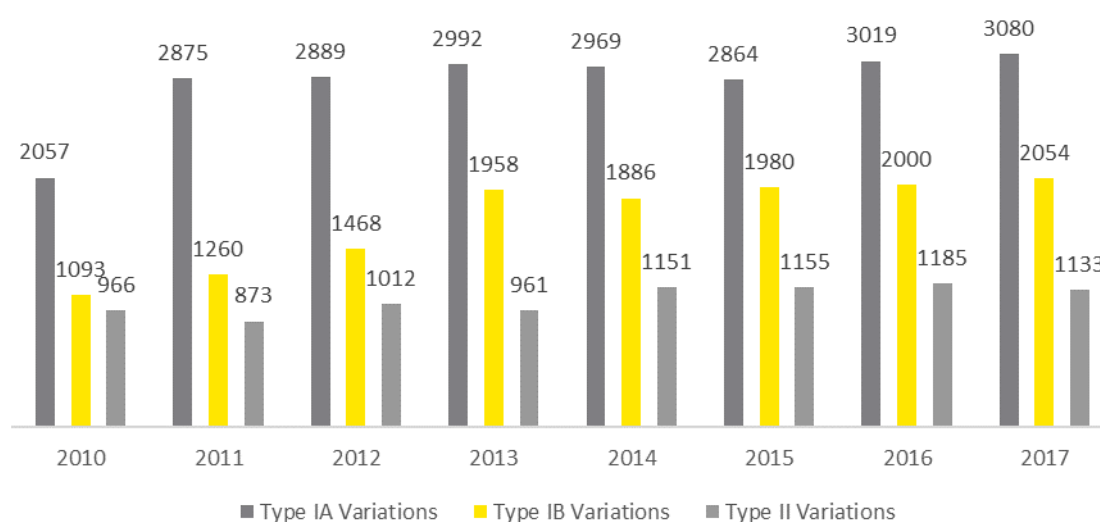
<sup>116</sup> EMA, Annual Activity Reports 2013-2017

<sup>117</sup> EMA, Annual Activity Reports 2013-2017

requirements, RMPs have the same format for all products. However, the pharmaceutical industry stakeholders interviewed, as well as 3 NCAs and 5 experts have questioned the necessity of full RMPs for generic products. As the active substances of these products have been on the market for a long time and are likely detailed in the pharmacopeia, a full safety profile and studies on the risks pose an unnecessary burden. Instead of studies on substances that have already been tested for decades, a reference to the pharmacopeia, which lists the relevant safety information, would simplify the process. This is the case both for the NCA, which needs to assess and evaluate additional information, as well as for the MAH, which needs to fill out and provide additional documents with information that is readily available to the public.

The third area where an efficiency gain exists is the administrative requirements of **variations**. Currently, variations present a high workload as every type of variation requires an approval by the regulatory authority. This entails around 6,000 administrative processes per year, as the number of variations has slightly grown over the study period, especially during the early years. Type IA variation amount to around one half of all variation, followed by Type IB variations, which make out around one third of the total.

**Figure 81: Evolution of variations received<sup>118</sup>**



**Whilst it is clear that major variations (Type II) can require an extensive assessment, minor ones falling under Type IA, such as the change of the address of a company, could be done in a simpler way.** This is supported by all types of stakeholders:

- ▶ Pharmaceutical industry stakeholders interviewed noted that a simple variation poses a very high administrative burden and called for a system where they could directly modify the data. Especially for products authorised under the MRP/DCP, the administrative burden was excessive, as certain administrative documents need to be prepared for each of the involved countries, i.e. up to 31 times.
- ▶ The EMA secretariat noted that whilst there had been a reform of variations, this had not achieved the goal of reducing the administrative workload.
- ▶ This view is shared by NCAs, as an initiative was sponsored by the HMA, the HMA Regulatory Optimisation Group (ROG) that reviewed how the administrative burden concerning Type IA variations could be reduced. As Type IA variations are the most frequently used variations, a reduction on their administrative burden could entail significant efficiency gains.

The recently drafted revised legislation on veterinary medicinal products<sup>119</sup> provides a potential simplification that could also increase efficiency regarding human medicines. The new legislation

<sup>118</sup> EMA, Annual Reports 2010-2017

<sup>119</sup> Regulation (EU) 2019/6

foresees two types of variations, variations requiring assessment and variations not requiring assessment. For variations not requiring assessment, marketing authorisation holders need to record the change in the product database within 30 days following implementation. As the link is directly between the MAH and the database, the administrative burden of submitting documentation to the NCAs is no longer exists. Upon entry into the database, the competent authority still informs the MAH if a variation is approved. If the system proves to be successful, it could be adapted for human medicines as well, rendering the process of variations more efficient. If this is the case, the type of variations no requiring assessment would need to be exactly defined, requiring an overall update of the variation classification guideline, an issue that was also raised by the previously mentioned HMA ROG.

## 7. Work Package 5: Support Activities

The aim of this Work Package is to examine the extent to which support activities effectively and efficiently succeeded in supporting the regulatory network's core activities. In this regard, the study examined support activities relating to telematics as well as communication.

In detail, this section aims to answer three evaluation questions:

1. Are telematics contributing to an effective functioning of the whole system?
2. Are telematics contributing to an efficient functioning of the System?
3. Are the communication activities contributing to an effective functioning of the whole system?

### Synthesis

**EMA Telematics provide significant added value**, and tools such as the Eudravigilance database are a strength of the system. EMA recognised the importance of the Telematics and has made considerable improvements over the past years such as the implementation of a new governance mechanism. Nonetheless, it needs to be ensured that the various tools function properly.

- ▶ User-friendliness and interoperability of Telematics could be improved, especially related to shared access to documents.
- ▶ The large amount of different telematics, 23 in total, could be consolidated, which would provide both security and efficiency gains.

Looking into the future, EMA will need to ensure that it has enough and relevant expertise in-house to develop and maintain solutions for future challenges and mitigate the risk of being dependent on external providers. This is especially important in light of the rise in importance of big data, as the incorporation of real-world data could significantly contribute to a simplification of the system.

Through its dedicated framework for **communication**, EMA sets clear goals to achieve for an effective functioning of the system. EMA has significantly increased its communication efforts since the last study. Overall, the mechanisms in place contribute to achieving the objective of making information related to marketing authorisation procedures available to the stakeholders and public as much as possible.

- ▶ An important tool in the process is the EMA website, which serves as an easily accessible hub of information and receives strong support (95%) from all types of stakeholders.
- ▶ EMA has also increased its efforts to communicate publicly, most recently through the public hearings.

The management of communication activities is efficient on an operational level, and greatly facilitates the overall function of the system through easy access to information.

A minor area of improvement concerns ensuring the large amounts of information provided are clearly structured and categorised, to ensure transparency is not diminished by too much information.

## 7.1. Are telematics contributing to an effective functioning of the whole system?

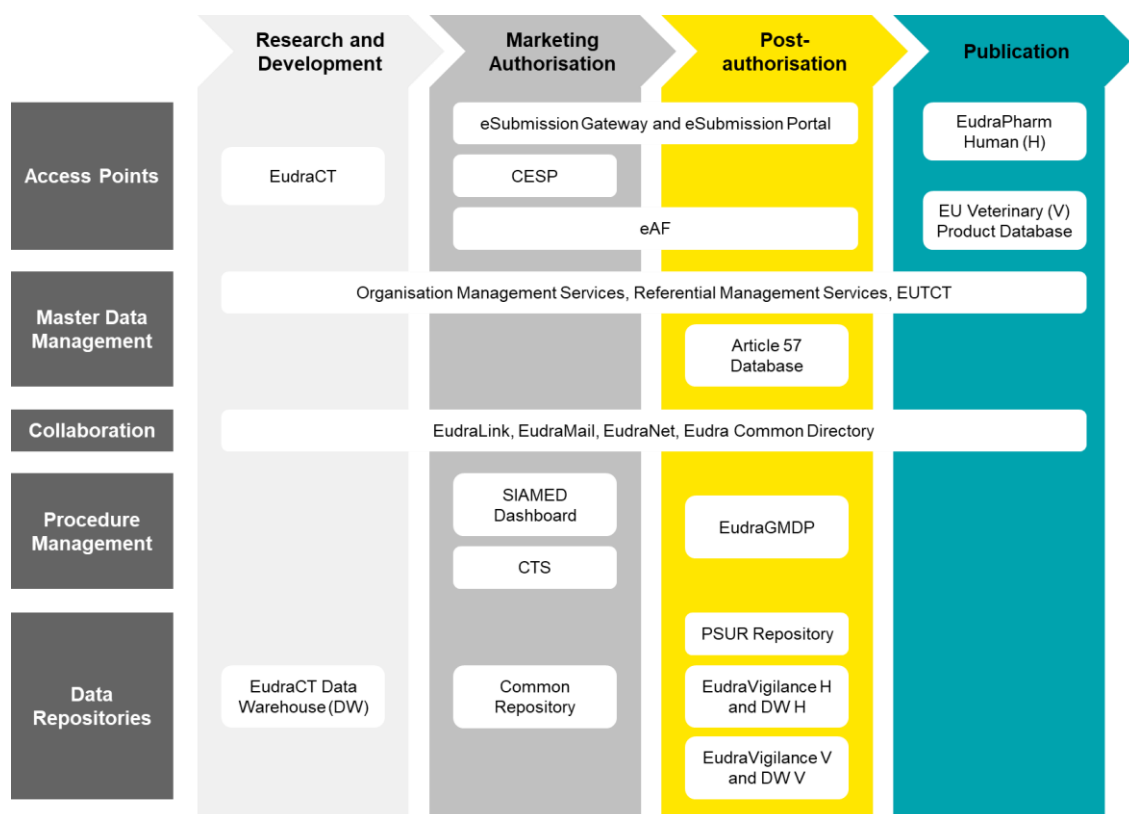
### 7.1.1. The use of telematics is contributing to an effective functioning of the network's activities

EU Telematics is “the collective name for a joint endeavour in the context of the regulation of medicines for human and veterinary use between the European Commission, the European Medicines Agency and national competent authorities”<sup>120</sup>. Through EU Telematics, the Network aims to maintain common information technology (IT) services to implement European pharmaceutical policy and legislation. The vision for EU Telematics is defined as follows.

*“A European IT collaboration that will deliver a broad range of cost-effective, efficient and interoperable services to the European Medicines Regulatory Network and to its stakeholders that improve the quality and effectiveness of their business activities.”<sup>121</sup>*

The EU Telematics consists of **23 IT tools** supporting the authorisation processes of medicines in the EEA. Whilst some Telematics such as the EudraNet or EUTCT are used throughout the whole procedure from research and development to publication, others are designed for a specific phase such as the Eudravigilance databases. The figure below presents an overview of which Telematics are used by the Network for which phase and task. A full list of Telematics as well as a brief explanation of each tool can be found in the annex. The figure below presents an overview of the different Telematics in relation to their function and use.

**Figure 82: Telematics used by EMA grouped by phase / task<sup>122</sup>**



<sup>120</sup> EMA, Website (July 2019)

<sup>121</sup> EU Telematics Strategy 2014-2016

<sup>122</sup> EMA, Website (July 2019)

**Telematics performance is measured by availability indicators rather than indicators with an end-user perspective.**

Performance indicators were put in place by the EMA Secretariat. Indicators show that the targets identified seem to be achieved or exceeded, with the exception of two indicators in 2014. The figure below presents an overview of these performance indicators:

**Table 11: Telematics Indicators<sup>123</sup>**

	Result	Target	Result	Target
	2014		2015	
Telematics and corporate IT systems availability against Agency working hours	99%	98%	98%	98%
Critical (resolution time: 4 hours)	46%	80%	100%	80%
Severe (resolution time 1 business day)	50%	80%	100%	80%
Important (resolution time 10 business days)	91%	80%	92%	80%
Minor (resolution time 120 business days)	99%	80%	100%	80%

	Result	Target	Result	Target
	2016		2017	
Availability of Telematics IT systems (%of time)	100%	98%	99%	98%
Availability of corporate website (%of time)	100%	98%	100%	98%
Availability of corporate IT systems (%of time)	100%	98%	100%	98%

Between 2015 and 2016 indicators related to Telematics used for activity reporting have been redefined. Whilst the reporting was focused on incident resolution time and IT systems availability until 2015, only the availability is reported after 2016. **To measure and monitor the performance of Telematics services, additional indicators (such as incident resolution, data transferred between Telematics, volume of Telematics usage, etc.) are necessary.** Moreover, the IT systems availability could be measured from an end-user perspective to report the perceived availability (such as time for an end to end process execution) more precisely.

Concerning the use of telematics, the majority of NCAs (19 out of 21) agreed that there had been a positive evolution in the use of telematics over recent years, thus increasing the contribution to an effective functioning of the network. This is further confirmed by scientific literature, such as Alvarez et al. (2010) who found that statistical signal detection procedures used with the EudraVigilance database can lead to a quicker detection of ADRs.<sup>124</sup>

**Whilst the recent developments in telematics were identified as positive, the “piecemeal approach” could be replaced by the use of an overarching system.**

As previously stated, EU telematics currently consist of 23 different IT tools, many of which are not interoperable. Furthermore, each NCA in the Network tends to also have their own IT tools and databases. This presents **two vulnerabilities of the system**. Firstly, developments in Telematics and IT tools require the involvement of all stakeholders to ensure successful implementation. Secondly, interlinkage and interoperability between the different IT tools need to be ensured as much as possible, to facilitate operation in the complex environment of multiple tools, processes and stakeholders.

- ▶ Regarding **vulnerability**, some stakeholders from NCAs considered it essential that IT experts from NCAs participate in the elaboration of a new overarching system in order to ensure successful implementation. Several NCAs through the written questionnaire recommended having a collective or joint governance of projects addressed by the EMA and HMA. A need was also identified by stakeholders to improve the transparency of decisions on telematics development and the steering of projects to mitigate against the risks of telematics initiatives not supporting efficiency in the regulatory processes as expected.
- ▶ Regarding **interoperability and cooperation**, interviews found that work is needed in order to optimise the use of SharePoint and/or database repositories highlighting the need to make telematics more user-friendly. Currently, the difficult user interface can at times prevent easy access to stored information due to information being stored in different tools and not easily

<sup>123</sup> EMA, Annual Activity Reports 2014-2017

<sup>124</sup> Alvarez, Y., Hidalgo, A., Maignen, F., & Slattery, J. (2010). Validation of statistical signal detection procedures in EudraVigilance post-authorization data. *Drug safety*, 33(6), 475-487.



transferable between areas. This was identified by stakeholders interviewed during case studies as a point of improvement related to knowledge management overall within the network, to address the need of effective access to information.

More specifically, experts and NCAs underlined the lack of tools that allow work to be undertaken horizontally on the same documents. A common IT SharePoint workspace could be developed for the centralised procedure in order to allow, for instance, rapporteurs and co-rapporteurs from the CHMP to work on the same document in parallel, such as for a joint assessment report.

**Different stakeholders stressed that the development of telematics is a key challenge for the future as well as ensuring the right level of internal IT expertise.**

The sentiment was shared by both NCAs as well as stakeholder umbrella organisations. In light of big data becoming ever more important and systems becoming more complex, it will be essential for EMA to develop their quantitative and analytical expertise and offer. As previously mentioned, the FDA has been running a dedicated programme on big data since 2008, which has been reinforced in 2019. The Japanese PDMA also launched a dedicated programme on collecting data post authorisation, the MIHARI programme, in 2013. Telematics will have to be developed to ensure that they can handle and address the challenges and opportunities big data poses. At the same time, it will be important to keep the end-users in mind, focusing on user friendliness and compatibility between systems.

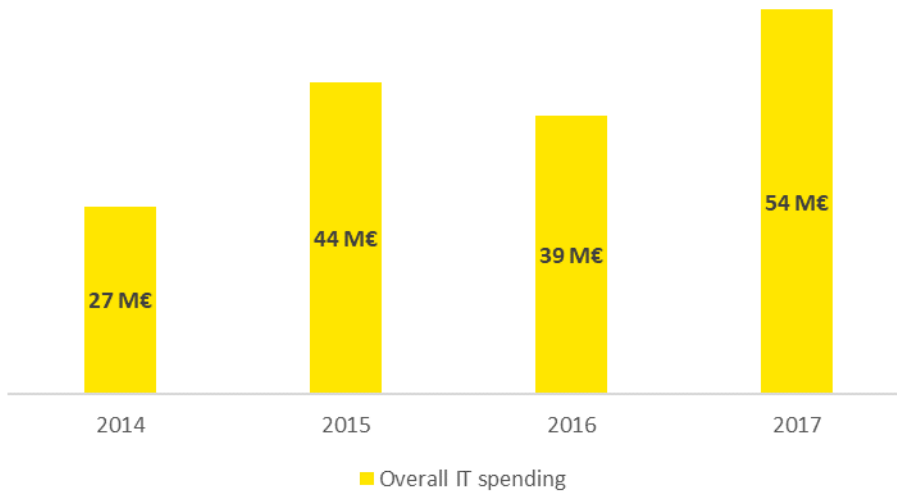
Regarding the competency framework, there are no gaps related to the necessary IT skills. However, in the long-term, a potential issue regarding capacity may arise if strong IT architecture skills are not present and developed as an in-house asset. In fact, when EMA needs to deliver efficient, interoperable and integrated IT systems, such projects would require considerable expertise related to their architecture. Therefore, strong IT architecture skills are needed within EMA and cannot be delegated to consultants. This is necessary to ensure and maintain a strong knowledge base in the area to address potential issues rapidly as well as to reduce the risk of dependency on external organisations.

## 7.2. Are telematics contributing to an efficient functioning of the System?

### 7.2.1. The budget dedicated to Telematics has increased, whilst staff numbers have remained constant

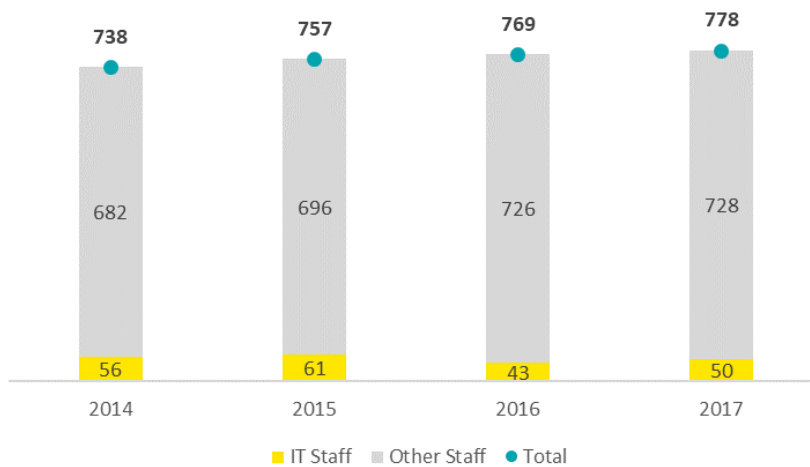
When looking at the IT budget of EMA, the special environment in which EMA operates needs to be kept in mind. The Telematics, which account for around 50% of EMA IT expenditure, are not only used by the agency itself but also by the network as a whole, including the NCAs of all 31 Member States. This means that EMA provides an IT system for a far larger field of stakeholders than personnel within the Agency. Furthermore, for many of the EMA activities, whether they are related to pre-, initial or post-authorisation, Telematics and IT systems play a crucial role in the process.

**Figure 83: EMA IT expenditure<sup>125</sup>**



**IT spending increased by 66% between 2014 and 2015.** This increase can be partly explained by an overall revision of the Telematics governance as well as by an increase in the number of telematics. The increase between 2016 and 2017 can, in part, be attributed to the relocation costs associated with the move of the agency to Amsterdam.

**Figure 84: EMA IT staff<sup>126</sup>**



Over the same time period, the staff dedicated exclusively to IT support has stayed relatively constant. This stands in contrast to the increase in telematics within the system, both in number as well as in importance. As mentioned above, it underlines the need **to internalise skills as a point of attention.**

<sup>125</sup> EMA, Annual Activity Reports 2014-2017, IT spending for 2017 includes relocation costs to Amsterdam

<sup>126</sup> EMA, Annual Activity Reports 2014-2017

**Table 12: EMA IT & Telematics resources<sup>127</sup>**

	2014	2015	2016	2017
EMA Information technology FTEs	56	61	43	50
EMA FTEs	738	757	769	778
EMA IT spending	26 569 066	44 088 052	39 303 751	54 409 000
<i>EMA IT spending per employee</i>	<b>36 001</b>	<b>58 240</b>	<b>51 110</b>	<b>69 934</b>
Number of Telematics information services provided by EMA	16	20	22	23
<i>EMA IT spending per Telematics information services provided by EMA</i>	<b>1 660 567</b>	<b>2 204 403</b>	<b>1 786 534</b>	<b>2 365 609</b>
Expenditure on Business related IT Projects	7 335 865	14 105 978	12 962 000	20 997 000
Number of ongoing Telematics IT projects where EMA is the delivery organisation	19	18	13	11
<i>EMA Expenditure on Business related IT Projects per IT Projects</i>	<b>386 098</b>	<b>783 665</b>	<b>997 077</b>	<b>1 908 818</b>

**At first sight, the comparison of EMA IT spending according to international standards points to potential efficiency gains though its broad reach must be considered.**

EMA IT spending per employee is between EUR 50,000 and EUR 70,000. As a point of comparison, the 2018 Gartner report (IT Key Metrics Data) for Governments (National/International) reports an average IT spending per employee of USD 20 526. The report is used by the EMA Secretariat as a benchmark of IT spending and can lead to the interpretation that EMA lags behind.

However, the ratio calculated as a comparison is solely based on EMA employees. It does not take into account the fact that NCAs also make use of the EMA IT systems. Hence, the overall target group is much larger than the agency itself. Although an exact measurement is not possible due to NCAs having their own IT costs as well, if EMA costs were to be spread across the system, the ratio would be substantially lower. Furthermore, the authorisation of medicines requires many IT systems in some areas. In post-authorisation activities for example, databases play a key role to the functioning of the system. As such, it is likely that EMA IT expenditure is higher than that of other public institutions, in which IT may be used to facilitate day-to-day operations, but there is no need to create and maintain specific tools which are essential to the functioning of the system.

7.2.2. Whilst progress has been made in the governance, there are still potential efficiency gains related to telematics

#### **Efficiency is a key area for EU Telematics.**

According to the EU Telematics Strategy 2015-2017, one of the strategic business goals of EU Telematics is to improve efficiency through seeking opportunities for technology to maximise efficiency in regulatory processes that will benefit both partners within the Network and their stakeholders. For example, the Eudravigilance database aims to facilitate the electronic exchange of individual safety reports, early detection and evaluation of signals as well as product information. A unique access point for data and processes for the whole network provides significant efficiency gains compared to a scenario where each NCA uses different systems. Against this baseline, all stakeholders agreed that Telematics play an important role in contributing to the efficiency of the system. Nonetheless, there are some areas of improvement as elaborated further below.

#### **The Network has overcome challenges in relation to the Telematics governance structure**

Interviews conducted with NCAs indicated that before 2014, the governance structure in place was very complex. Concerns were raised regarding the extent to which the EMA could efficiently deliver systems in the interest of the whole Network. This led to the decision to establish a new strategy and governance model in 2014/2015. The Telematics Office was created in order to improve governance and efficiency by facilitating communication and the achievement of shared objectives. The EU Telematics Management Board was also created with a mix of business and IT groups from the network, the EMA and the European Commission. The positive effects of the new strategy were noted by all members of the Network and were recognised in EMA Annual Reports of the Management Board, underlining the improvements that were made.

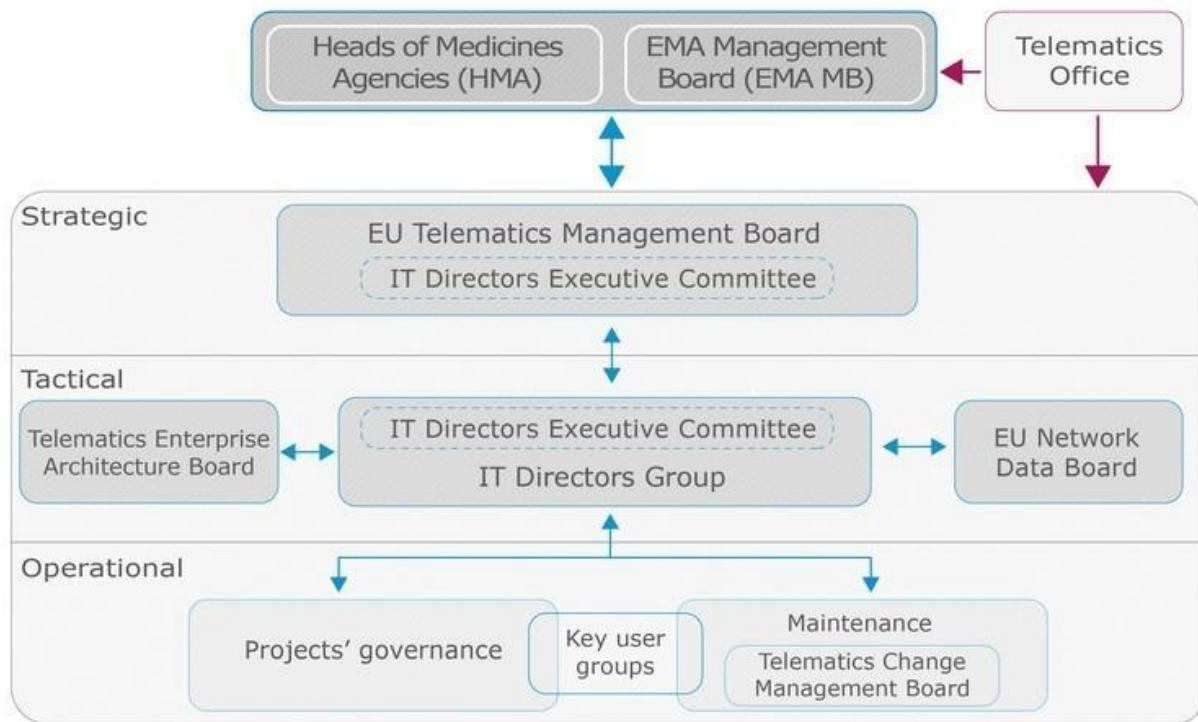
The new EU Telematics governance has three main objectives:

<sup>127</sup> EMA, Annual Activity Reports 2014-2017, Budget 2014-2017, IT spending for 2017 includes relocation costs to Amsterdam

- ▶ To foster collaboration across the EU regulatory network by setting up and maintaining a coalition of willing partners to develop, implement and maintain common IT services;
- ▶ To maximise efficiency in communication around the development and operation of IT for the EU regulatory network;
- ▶ To become a platform for all ongoing IT activities for the EU regulatory network over time.

The figure below presents an overview of the Governance structure in place.

**Figure 85: EMA Telematics Structure<sup>128</sup>**



Whilst the overall effectiveness of telematics can contribute to the efficiency of the system as a whole, the need to ensure that **SharePoint** and **knowledge management** are improved demonstrates the ability to improve the overall efficiency of the system. Some stakeholders have noted that the EMA telematics put in place may not be fully compatible with national systems, which can lead to a duplication in work and thus a decrease in efficiency.

**In general, EU Telematics are constantly evolving and developing, alongside changes in legislation and technological innovation.**

This means that on a regular basis, EMA is required to deliver new business processes. These processes generally aim to contribute to the efficiency of the system. This has an effect on the overall number and types of telematics required. Thus, the large number of telematics is the result of new legislation put in place over the past 20 years. Optimisation could lead to economies of scale by allowing stakeholders to access multiple features through a smaller number of IT tools. Furthermore, it would limit the risks associated to data transfer between systems.

There have also been some issues with the full functionality of Telematics, as the development of some databases has experienced delays. Four of the NCAs pointed to the Eudravigilance database, in which the search function is not fully developed, making it difficult and time-intensive to find the relevant case reports. Other stakeholders pointed out that the Article 57 database may not always be reliable, with some missing or outdated entries. This requires data taken from this database to be cross-checked with other existing databases, which leads to a duplication of work efforts.

<sup>128</sup> EMA

This points to a larger challenge pointed out by NCAs, namely consistency across databases. For Telematics to function effectively and to decrease the workload and increase efficiency, it is imperative that databases including similar data use the same datasets and vocabulary. 3 NCAs interviewed during the case studies have reported that this is not always the case.

**Whilst the Telematics in place at the moment help contribute to the system functioning efficiently, it will be important to ensure that systems develop with the general digitisation of the healthcare sector.**

Various stakeholders, experts and NCAs, have stressed that the network is currently falling behind in the development of IT systems. As these systems are a strategic business component, not addressing them in a timely and agile manner will likely result in a decreased efficiency of the network in the near future. This is especially important with the rising importance of big data. Incorporating real world data could ultimately lead to a simplification of marketing authorisation processes, especially in the field of post-authorisation processes. One NCA specifically stressed the importance of the system to develop and evolve to be able to use real world data in the future.

## 7.3. Are the communication activities contributing to an effective functioning of the whole system?

### 7.3.1. The communication strategy and tools are relevant to meet stakeholders' needs

**EMA is tasked by its founding Regulation (EC) 726/2004 to communicate about its work to partners, specific stakeholder groups and the general public.**

EMA's Framework Strategy for External Communications 2016-2020 provides guidance to EMA's communication activities, identifying a number of key goals.

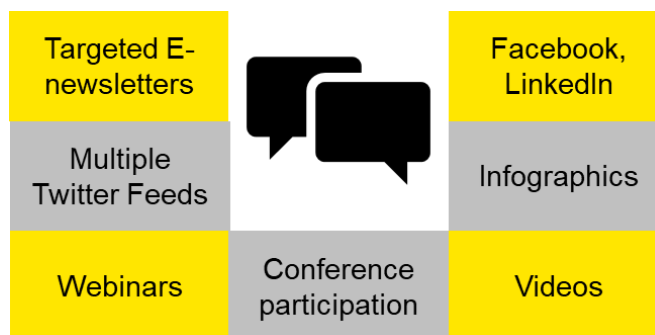
- ▶ Providing EEA citizens with reliable, timely and up-to-date information on EEA medicines so that they can use them safely;
- ▶ Promoting public knowledge and understanding on how medicines are regulated in the EEA to ultimately foster public confidence and trust in the EU regulatory system;
- ▶ Strengthening collaboration and partnership with national competent authorities and other partners;
- ▶ Reaching out to new and less experienced audiences (e.g. SMEs) to help foster the development of medicines, for example, through targeted communication using the right channels and clearly defined engagement strategies;
- ▶ Maximising the use of digital tools and channels;
- ▶ Increasing public health impact through simplified, understandable messaging, e.g. by developing new types of user-friendly communication tools (e.g. videos and infographics), increased use of lay language in information.

Additionally, the EMA Multiannual work programme to 2020 proposes a number of performance indicators to contribute to the objective of ensuring effective communication of, and within, the network. These performance indicators were to be implemented by 2020. EMA has successfully worked towards these indicators and achieved a number of targets, such as the creation of the Framework Strategy for External Communications, the biennial implementation of the perception survey, the upgrade of the EMA corporate website and the implementation of public hearings. The successful achievement of the indicators presents a first indication of the effectiveness of EMA communication activities.

**EMA has significantly increased its focus on communication and transparency over the course of the study period.**

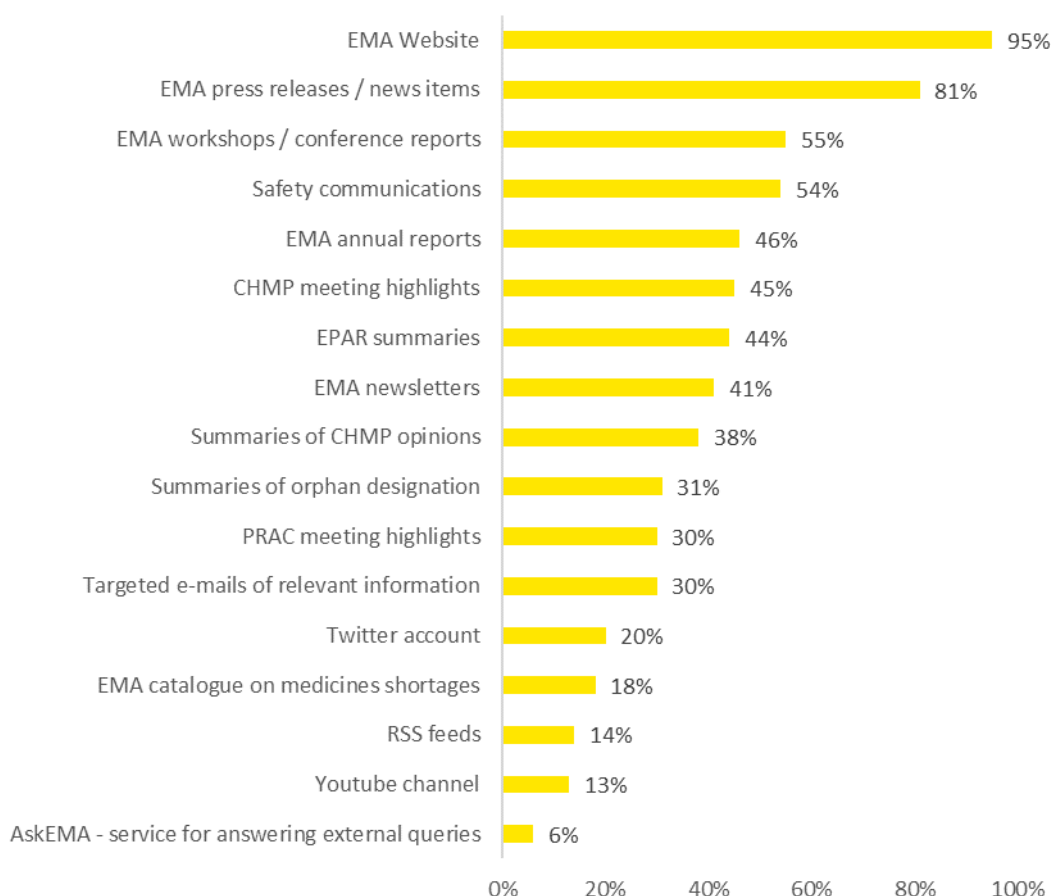
EMA makes use of a number of communication tools, both online (e.g. E-newsletters, Facebook) as well as offline (e.g. Conferences). The figure below presents the communication tools used by EMA.

**Figure 86: EMA Communication Tools<sup>129</sup>**



When stakeholders were asked about which communication tools and materials they had used, it became clear that some are much more frequently consulted than others. The most frequent answer was the EMA website, with 95% of respondents answering positively. This was followed by the EMA press releases and news items, with 81%, and EMA workshop and conference reports, with 55%. The least commonly used tools were the YouTube channel, with 13% and the AskEMA tool, with 6%. Whilst the AskEMA tool seems to be intended only for specific request, which could explain low numbers, this is not the case for the YouTube channel.

**Figure 87: EMA communication tools and materials used<sup>130</sup>**



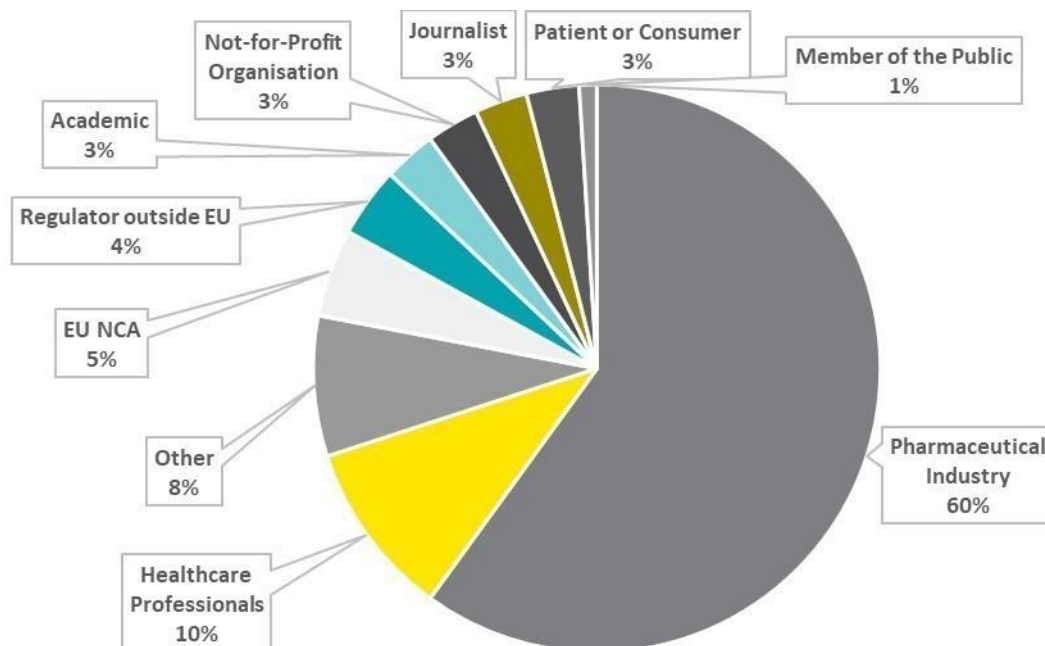
Concerning the use of the **EMA Website**, according to the 2017 EMA Communication Perception survey, the large majority of visits to the EMA Website were pharmaceutical companies. The pharmaceutical

<sup>129</sup> EMA, Communication Perception Survey 2017

<sup>130</sup> EMA, Communication Perception Survey 2017

industry accounts for 60% of the visits to the Website followed by Healthcare Professionals with 10% of the overall visits.

**Figure 88: EMA web visitor profile (2017)<sup>131</sup>**



**The EMA website is an effective source of information on EMA.**

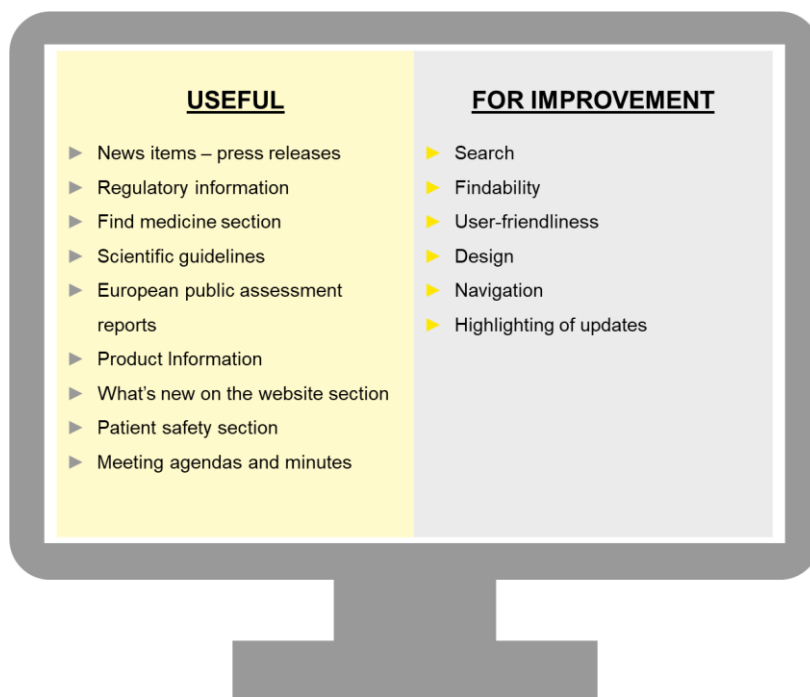
When consulted through interviews, all stakeholders from industry to NCAs seemed to be satisfied with the EMA website. Interviewed partners mentioned that the information provided was complete and the search function worked well. They especially highlighted the evolution of the website, noting that whilst previously information on EMA activities was not easily available and the system seemed to lack transparency, the website now provides access to all the relevant information. This was confirmed by the findings of the communication perception survey, where users pointed out a few features that they find very useful, such as press releases, regulatory information and scientific guidelines.

At the same time, some areas of improvement for the website were identified. These mainly related to searching and finding information and user-friendliness. Due to the near to complete transparency of information, it can be hard to discern the different types of information published, especially regarding relevance and importance. Whilst publishing all information supports transparency, it also risks an information overflow, which could again have a negative effect on transparency. Hence, a clear structure and a user-friendly design needs to be ensured. The figure below presents the complete list of useful items and areas for improvement from the 2017 EMA communication perception survey.

<sup>131</sup> EMA, Communication Perception Survey 2017



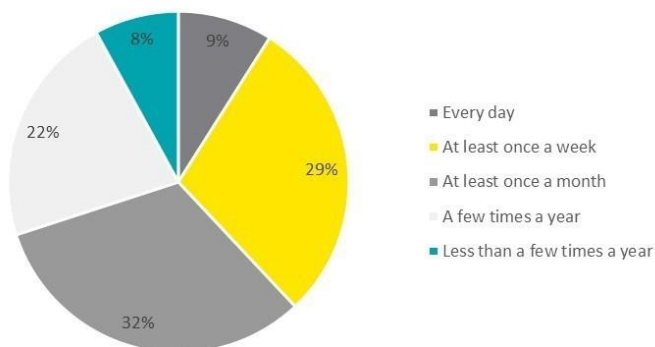
**Figure 89: Feedback on the EMA website<sup>132</sup>**



**Communication tools are used on a regular basis.**

According to the 2017 EMA communication perception report, when asked how many times they use EMA communication tools, the large largest group of stakeholders<sup>133</sup> answered at least once a month (32%), whilst 29% stated at least once a week and 9% stated every day.

**Figure 90: Use of EMA communication tools by stakeholders<sup>134</sup>**



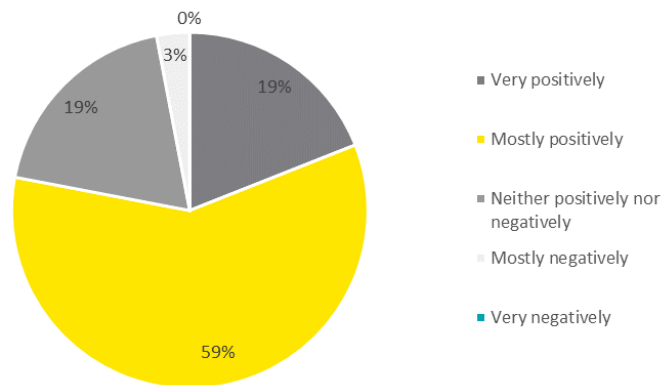
The large majority of stakeholders rated the quality of EMA’s communication to the public positively. 19% stated they found it very positive, whilst 59% stated they found it mostly positive. Only 3% of stakeholders had a negative opinion of EMA communication quality.

<sup>132</sup> EMA, Communication Perception Survey 2017

<sup>133</sup> Stakeholders refers to academia, healthcare professional and patient organisations, pharmaceutical industry associations, media and health technology assessment bodies.

<sup>134</sup> EMA, Communication Perception Survey 2017

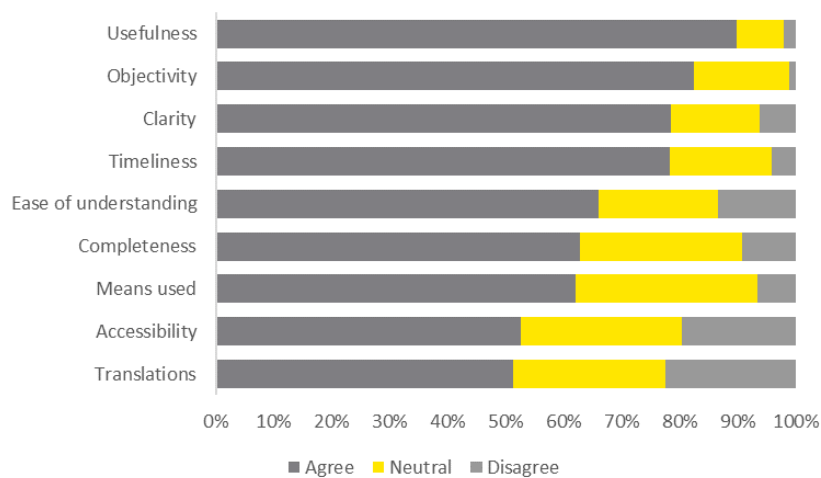
**Figure 91: EMA communication to the public<sup>135</sup>**



**When looking at various quality parameters of the EMA communication tools, information is useful and clear.**

Stakeholders most frequently agreed that the information provided was useful (88%). This is followed by objectivity (80%) and clarity (77%). On the bottom end of the scale, only 51% found the information to be easily accessible and only 39% were satisfied with the translations provided. The graph below provides an overview, without taking into account respondents that responded, “I don’t know.” The findings presented in the graph were confirmed by pharmaceutical companies, patient organisations and NCAs. All of them confirmed that the communication by EMA was effective and clear.

**Figure 92: Quality parameters of EMA communication<sup>136</sup>**

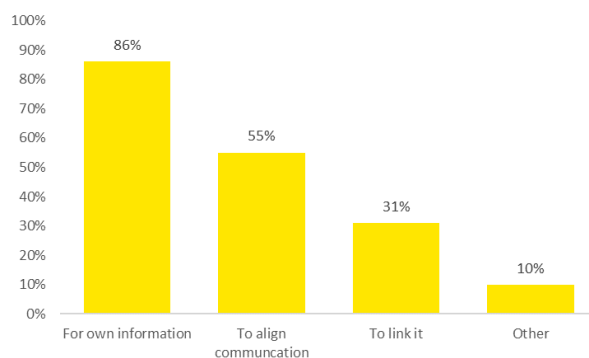


Actors such as NCAs, EU Agencies and institutions as well as other EU Authorities reported a high uptake of EMA Communications. It is interesting to note that whilst 86% of EMA partners noted that they used EMA communications for their own information, 55% of partners reported using them to align their own statements, pointing to a potential streamlining effect.

<sup>135</sup> EMA, Communication Perception Survey 2017

<sup>136</sup> EMA, Communication Perception Survey 2017

**Figure 93: Use of EMA communications by partners<sup>137</sup>**



Pharmaceutical companies and NCAs consulted during the study were satisfied with the number of **external communication events** organised by EMA. NCAs echoed the satisfaction with external communication. Patient organisations welcomed the initiatives taken by EMA, such as the recently organised public hearings and noted that EMA was on a good path. However, they stressed that these efforts should be expanded and continued.

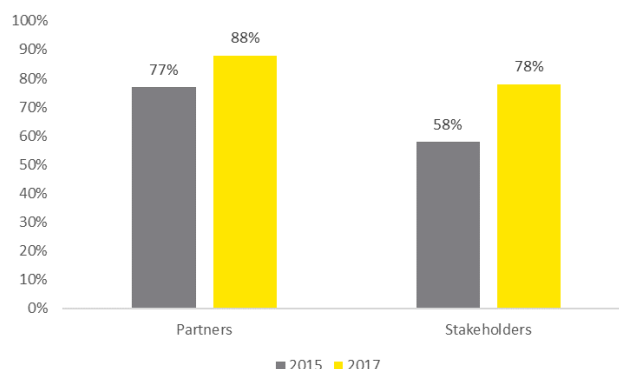
**Box 7: Clinical data publication**

In October 2016, EMA started publishing clinical data submitted by pharmaceutical companies in an effort to make more information available to the public. EMA was the first regulator worldwide to take this step, despite this being one of the *‘most controversially discussed topics among regulatory agencies, the pharmaceutical industry, journal editors, and academia’* according to Koenig et al. (2015)<sup>138</sup> However, as part of the business continuity plan and the move to Amsterdam, this was suspended in July 2018 until further notice. Industry stakeholders consulted during the study noted that the process was extremely burdensome to both regulators and industry.

Stakeholders are satisfied with **internal communication**. Experts consulted through the online survey also considered internal communication between network actors to be satisfactory, with 19% considering it to be satisfactory to a high extent and 64% considering it to be satisfactory to some extent. The majority of NCAs were satisfied with the overall level of internal communication between network actors.

**Overall satisfaction with EMA communications has increased over the past years, both among partners and stakeholders.** The percentage of partners satisfied with EMA communications increased by 11% between 2015 and 2017, whilst the satisfaction among stakeholder increased by 20% in the same timeframe.

**Figure 94: Satisfaction with EMA communications<sup>139</sup>**



<sup>137</sup> EMA, Communication Perception Survey 2017

<sup>138</sup> Koenig, F., Slattery, J., Groves, T., Lang, T., Benjamini, Y., Day, S., Bauer, P. & Posch, M. (2015). Sharing clinical trial data on patient level: opportunities and challenges. *Biometrical Journal*, 57(1), 8-26.

<sup>139</sup> EMA, Communication Perception Survey 2017

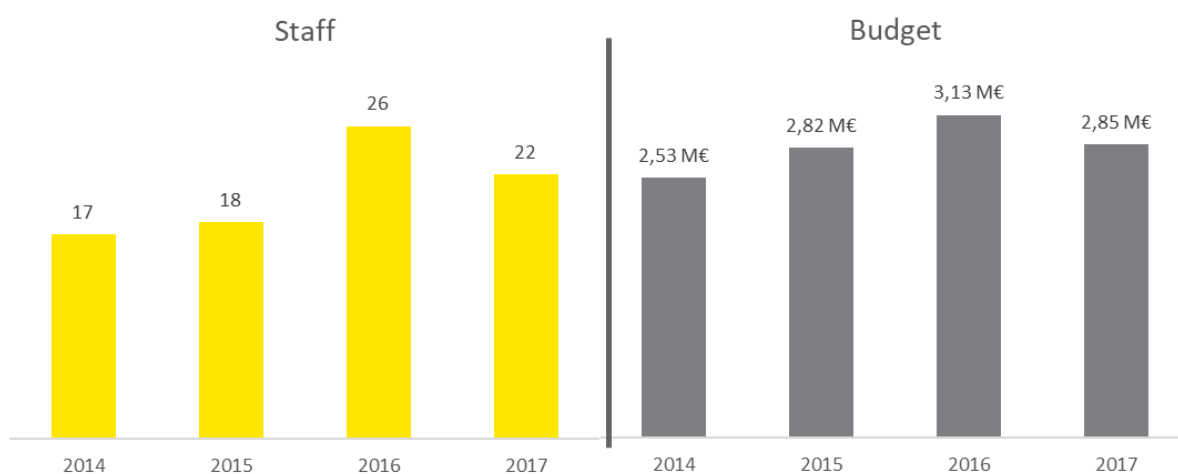
## 7.4. Are the communication activities contributing to an efficient functioning of the whole system?

7.4.1. Despite a general overhaul of EMA communication activities, the communication budget did not increase significantly

**Resources devoted to corporate communication have only evolved slightly over the past years.**

Communication expenses have seen a slight increase over the past years, from EUR 2,53 million in 2014 to EUR 2,85 million in 2017. The same increase is seen regarding staff dedicated to corporate communication activities, which have increased from 17 in 2014 to 22 in 2017.

**Figure 95: Corporate communication staff and budget<sup>140</sup>**



The small change in budget and staff stands in stark contrast to the significant increase in communication activities as well as stakeholder satisfaction, as mentioned in the previous sections. This points to an overall efficient use of communication resources by EMA to support the system.

7.4.2. In general, communication efforts contribute to the efficiency of the system

**Significant development and improvement have occurred in EMA communication activities.**

This has led to overall efficiency gains within the system. Taking the example of the pharmaceutical industry, they have pointed out the immense added value of the revamped EMA website. Stakeholders from the industry interviewed noted that they found almost all of the information they needed easily on the EMA website, especially through the search function. This facilitation of access to important documentation contributed to faster access to information and an overall decrease in administrative burden. The same sentiment was echoed by the NCAs, which also pointed out the usefulness of the EMA website

<sup>140</sup> EMA, Annual Activity Reports 2014-2017

## 8. Conclusions and Possible Actions

As outlined in the Terms of Reference, the study should identify possible actions which could be taken to eliminate barriers and analyse the pros and cons of each action.

Based on the findings of the study, this section presents a number of potential actions. The actions are categorised into five areas, reflecting the part of the system they address. Within each of the areas, the actions are further grouped by topics. The structure is as follows:

- ▶ **Functioning of the Network**
  - Committee and Working Parties
  - Network expertise
- ▶ **Adequacy of the System**
  - Specific products
  - Coordination efforts
  - IT infrastructure
- ▶ **Supporting procedures**
  - Pre-submission procedures
  - Post-marketing authorisation procedures
- ▶ **Centralised Procedures**
  - Support to SMEs
  - Selection procedures
  - Procedural aspects
- ▶ **Decentralised Procedure / Mutual Recognition Procedure**
  - Interpretation and harmonisation
  - Timelines

The individual actions are presented in the format depicted in the table below. Each action is linked to specific findings, which are described in detail in the reference chapter identified. Furthermore, for each action, the relevant stakeholder is mentioned, and the pros and cons are briefly outlined. The pros and cons should be considered against the option of not taking the action and keeping the status quo.

Finding	Reference Chapter		
Potential action	Relevant Stakeholder	+	-

Some actions would require a change in the legislation. These are identified by the symbol §.

## Functioning of the network

The network is overall strong, relevant and directly contributes to the effectiveness and efficient of the procedures. It is appreciated by all stakeholders as a globally unique exercise of cooperation between Member States. Coordinated through the EMA Secretariat and the HMA it fulfils its duties as presented by the legislation successfully. Nonetheless, there are areas that could be improved. These most notably related to the setup and coordination between Committees and Working Parties as well as the expertise available within the network.

### Committees and Working Parties

<b>Finding 1 There are instances where COMP has to revise Orphan indications following the discussions of CHMP</b>			<b>3.1.1</b>
Organise structured exchanges between CHMP and COMP before the final decision on the indication is taken	EMA secretariat	Less divergences between different Committees / WP.	An additional effort by the EMA secretariat is necessary.

<b>Finding 2 Some temporary working parties go beyond their temporary designation</b>			<b>3.1.1</b>
Periodically review the number and scope of working parties, with a specific focus on temporary working parties and their status.	EMA secretariat	The system is quicker to react to eliminate WP that are no longer needed, or accordingly adjust the status of others.	A periodic review would entail an extra responsibility of the EMA secretariat as well as creating a framework for the review.

<b>Finding 3 CHMP capacity is limited (CHMP meets every month for 4 days). At centralised level, the same procedure is equally applied for generic and non-generic products (same timelines, same decision-making process, etc.) without taking into account the new/innovative character of the molecule</b>			<b>5.5.2</b>
Envisage a way to reallocate CHMP time on more critical/complex applications and innovative molecules (like for instance CAR-T CELL). For instance, confirmation through writing, adaptation of CHMP agenda, etc.	EMA	No change requires in the legislation	-

### Network expertise

<b>Finding 4 The network does not have a formalised mechanism on network to anticipate future challenges</b>			<b>5.1.4</b>
Move beyond ad-hoc flexibility and develop clear strategies on how to address future challenges. This could be built by combining the efforts taken by EMA and HMAs separately.	EMA / NCAs	Formalised exchanges will ensure the network is prepared for future challenges	A formalised mechanisms risks overlap with other, existing governance mechanisms.

**Finding 5 The network lacks expertise on integrating big data / real life data** **3.3.1 / 6.2.3 / 7.2.2**

In light of the rising importance of big data, a special focus should be set on developing big data expertise both within EMA as well as within NCAs. An effort should be made to incorporate real life data in important areas such as post-marketing authorisation monitoring.

EMA / NCAs	Data expertise will allow to exploit the benefits of the field, e.g. in monitoring of medicines through real life data.	Training of staff will require allocating dedicated resources to the field.
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**Finding 6 There still exist some discrepancies in expertise between Member States, smaller and newer MS not taking part as actively in procedures** **3.3.2**

Multinational teams should be developed further, and smaller MS should be encouraged to take a role in MNATs, to ensure their integration despite the capacity constraints they might naturally face.

CHMP	Expertise in smaller MS will be developed.	MNATs require more coordination.
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***Adequacy of the system***

The legislative and organisational system in place to support the activities of the network is adequate and contributes to the safety of medicines on the market. Exchanges between the different stakeholders within the system work well, and the working methods are adapted to ensure it functions successfully. However, there are certain products to which it is not perfectly adapted. Furthermore, coordination and IT infrastructure could be expanded and improved.

**Specific products**

**Finding 7 The system has difficulties handling products on the border of medicines and medical devices** **5.1.4**

In light of the rising importance of combination products, a task force should be created to consider potential solutions to address the issue (i.e. develop guidelines). This can be built on the recently launched public consultation by EMA.

EMA / European Commission	The network would be prepared for the rising importance of combination products.	-
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**Coordination efforts**

**Finding 8 There is little coordination with HTA bodies** **4.2.1/4.4.2**

Coordination between NCAs / EMA and HTA bodies should be developed as much as possible. This can be done by building on existing initiatives such as EUnetHTA and expanding and promoting

EMA / NCAs / HTA bodies	HTA and NCA cooperation would significantly speed up timelines and ensure that	Full coordination would require MS to transfer some competences to a central
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cooperation at national level. The proposal for a new legislation is a first step toward a better coordination.

	products that receive a marketing authorisation actually make it to the market and be reimbursed.	level, thus adapting legislation.
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**Finding 9 Coordination on addressing emergency needs in relation to medicine shortages is not formalised**

**6.2.1**

Building on recently launched pilot projects, coordination in addressing emergency needs should be formalised. Special focus should be put on the area of medicine shortages, where awareness is relatively low. A first step might be the development of best practices guidelines at a European level which could incite the Member States to cooperate more closely on the issue.

NCA, EMA, Commission National ministries	A formalised mechanism ensures better preparedness, especially since problems are likely to touch multiple Member States	Currently, emergency preparedness measure area national competency, formalisation at EU level would require harmonisation efforts.
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**IT infrastructure**

**Finding 10 In recent years, EMA has only published few Telematics performance indicators**

**7.1.1**

Publish more detailed Telematics performance indicators, similar to those published in 2014 and 2015. These could include incident resolution, data transferred between Telematics, and volume of Telematics usage.

EMA secretariat	More detailed indicators will allow to identify shortcomings more easily, ensuring a better functioning of the system.	Measuring more indicators require a more detailed and refined monitoring system.
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**Finding 11a The right balance between in house IT expertise and external providers should be kept.**

**7.1.1**

**Finding 11b Interoperability of different telematics within the system is not always given**

**7.1.1**

**Finding 11c Databases are not functioning optimally, e.g. EudraVigilance**

**7.2.2**

Build IT expertise in house by expanding the dedicated IT team. The team should develop interoperability of EMA IT systems, both among each other as well as with national databases. It could furthermore address existing issues that are identified, such as the functioning of databases. When implementing larger IT projects with the help of external expertise, ensure internal expertise is involved sufficiently to guarantee the project can be successfully maintained and developed in the future.

EMA secretariat	Building internal expertise will ensure EMA can better address existing IT issues and is prepared for future challenges such as big data.	In-house IT expertise requires more human resources and is costlier than relying on external contractors.
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## Supporting procedures

The procedures supporting the initial marketing authorisation procedures ensure an effective functioning of the system. Pre-submission procedures allow for refining applications and screening those that have little chance of authorisation at an early stage. Furthermore, constant exchange ensures that all parties work well together. At the same time, post-authorisation procedures provide an effective framework to monitor medicines that are already on the market and guarantee a high level of patient safety. Both areas nonetheless have certain issues that could be improved. Whilst pre-submission procedures could benefit from closer coordination and adaptation to innovation, post-authorisation procedures entail some areas of excessive administrative burden.

### Pre-submission procedures

#### Finding 12 Scientific guidelines are not always up to date, and thus slow to adapt to innovation

4.3.1

A 'shelf-life' for scientific guidelines should be introduced, which would mean every guideline needs to be reviewed after a certain period of time. The time period should be set according to the matter discussed by the guidelines, with innovative technologies being reviewed more frequently.

CHMP / EMA  
secretariat

More up to date guidelines improve information available to the industry, making applications better and thus decreasing resources needed to evaluate MAA.

A regular review requires additional effort from the CHMP

#### Finding 13 There is a risk of duplication of work in early advice between EMA and NCAs

3.1.4 / 4.1.3

Ensure there are no overlaps or duplication of work, making the whole process clearer for applicants. Do this by close coordination and using existing NCA mechanisms (innovation offices) in place to support any development of EMA outreach.

CHMP / EMA  
secretariat

Improved scientific advice to applicants, closer cooperation without duplication.

Additional coordination efforts are required

### Post-marketing authorisation procedures

#### Finding 14 Renewals contribute little to the system in light of various other pharmacovigilance procedures

6.3.2

§ Review the necessity of renewals, potentially reviewing the legislation similarly to the reform of the veterinary legislation.

European  
Commission

The system would be more efficient.

The change would require a change in legislation.

#### Finding 15 Risk Management Plans (RMPs) represent an unnecessary administrative burden for generic products

6.3.2

§ Eliminate RMPs for generic products, creating the opportunity to refer to active substance profiles in the pharmacopeia.

CHMP / EMA  
secretariat

The system would be more efficient.

The change would require a change in legislation.

**Finding 16 The Variations procedures, especially Type IA Variations, is very burdensome** **6.1.1/6.3.2**

§ Simplify the Variations legislation in line with the simplifications done for variations concerning veterinary medicines. This would notably include allowing MAH to make Type IA variations directly in the databases, without passing via NCAs.

CHMP / EMA secretariat

The system would be more efficient.

The change would require a change in legislation.

**Centralised Procedure**

The Centralised Procedure is a robust and well-defined procedure, that provides applicants with clarity and predictability regarding its scope and its timelines. It successfully relies on the expertise provided by NCAs and is the procedure of choice for innovative medicines. However, for SMEs, it can still be difficult to complete, due to its resource intensity. Furthermore, selection of rapporteurs as well as patient involvement could be made clearer. Finally, certain procedural aspects could be strengthened.

**Support to SMEs**

**Finding 17 SMEs still have trouble successfully completing a CP MAA** **4.1.3 / 5.5.2**

Building on the work of the SME office and the ITF, further increase support to SMEs during the procedure, creating a mechanism similar to PRIME for SMEs. The mechanism should at the same time take into account the reservations shown by the Ombudsman inquiry.

EMA Secretariat / NCAs

SMEs have a higher chance of successfully completing a MAA.

Closer cooperation invites doubt on independence, thus requiring adequate safeguards.

**Selection procedures**

**Finding 18a Patient selection procedures could be improved** **3.1.3**

**Finding 18b Rapporteurship designation could be made more transparent for NCAs** **5.4.2**

Further formalise selection criteria that are currently based on the discretion of the Chair/Executive Director to allow greater transparency and predictability.

EMA

Predictability for rapporteurs allows NCAs to better allocate resources, whilst patient selection criteria would increase transparency towards external stakeholders.

More formalised selection procedures limit the flexibility in specific cases.

**Procedural aspects**

**Finding 19 The 22-day review period by the Standing Committee is too long** **3.1.2**

Review to what extent the 22-day framework can be shortened, taking into account the 10-day framework which works well under the accelerated assessment. This would require some changes of the rules of procedure.

Standing Committee European Commission	Clarity before detail improves user-friendliness and ease of use.	Leaving out some details can open room for interpretation.
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<b>Finding 20a PDCO procedures could be strengthened, as identified by the 2018 action plan</b>	<b>4.1.2</b>
<b>Finding 20b Scientific advice given by the SAWP is not always aligned with PDCO opinions</b>	<b>3.1.1</b>

§ Ensure the shortcomings identified in European Medicines Agency and European Commission action plan on paediatrics are addressed, by strengthening the role of the PDCO and its coordination with other Committees and Working Parties and improving the handling and completion of PIPs.

EMA / European Commission	PDCO work would be more effective and PIPs would have a lower administrative burden.	A stronger PDCO may create a greater need for coordination with other Committees.
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<b>Finding 21 Companies cannot refer to existing documentation in MAA</b>	<b>5.5.2</b>
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Explore to what extent procedures could be simplified by allowing companies to refer to existing documentation in the MAA.

CHMP / EMA secretariat	Administrative burden would be reduced through limiting the number of documents to be submitted.	There is a risk of companies abusing the option, by excessively referring to previous documentation as well as a risk of existing documentation becoming outdated.
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### ***Decentralised Procedure / Mutual Recognition Procedure***

The DCP is a procedure providing applicants with the flexibility to choose the market for their product. It is generally quicker than the CP and the procedure of choice for generics. The MRP is an adequate procedure to deal with products already on the market in some Member States. Both procedures however, could benefit from a higher degree of harmonisation and from and more stringent respect of timelines.

### **Interpretation and harmonisation**

<b>Finding 22 Coordinating early scientific advice from different MS presents a burden to the industry</b>	<b>4.1.3</b>		
Create a mechanism in which scientific advice given from various MS is coordinated; through formalised exchanges or a system in which SA is aligned before it is provided to the applicant.	NCA's	Procedures are facilitated for applicants.	Additional efforts would be necessary from NCA's.

**Finding 23 Interpretation of EU legislation differs from one MS to the other. And MS are requesting additional information related to the national legislation leading to administrative burden for the applicants (for instance, forms differs from one MS to the other)** **5.5.3**

Identify inconsistencies and increase the work towards harmonising definitions and interpretation of EU legislation across Member States and encourage MS to align their requirements with existing guidelines.	CMDh HMA EMA	Procedures are facilitated for applicants.	
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**Finding 24 OTC / prescription status differs across MS** **4.1.3/5.1.2**

§ Increase the work towards harmonising definitions and categorisation of products across Member States. This could be facilitated through EMA adopting guidelines on European standards / best practices.	NCAs	Procedures are facilitated for applicants.	Significant harmonisation efforts are required.
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**Timelines**

**Finding 25 MRP / DCP timelines are not always respected** **5.2.3 / 5.5.3**

Review to what measures could be taken to ensure MRP / DCP timeline are better respected, both by NCAs and industry, through either allocating additional resources or formalising and redefining timelines.	NCAs	Industry stakeholders have more clarity on timelines.	Either more resources are required, or timelines would have to be extended.
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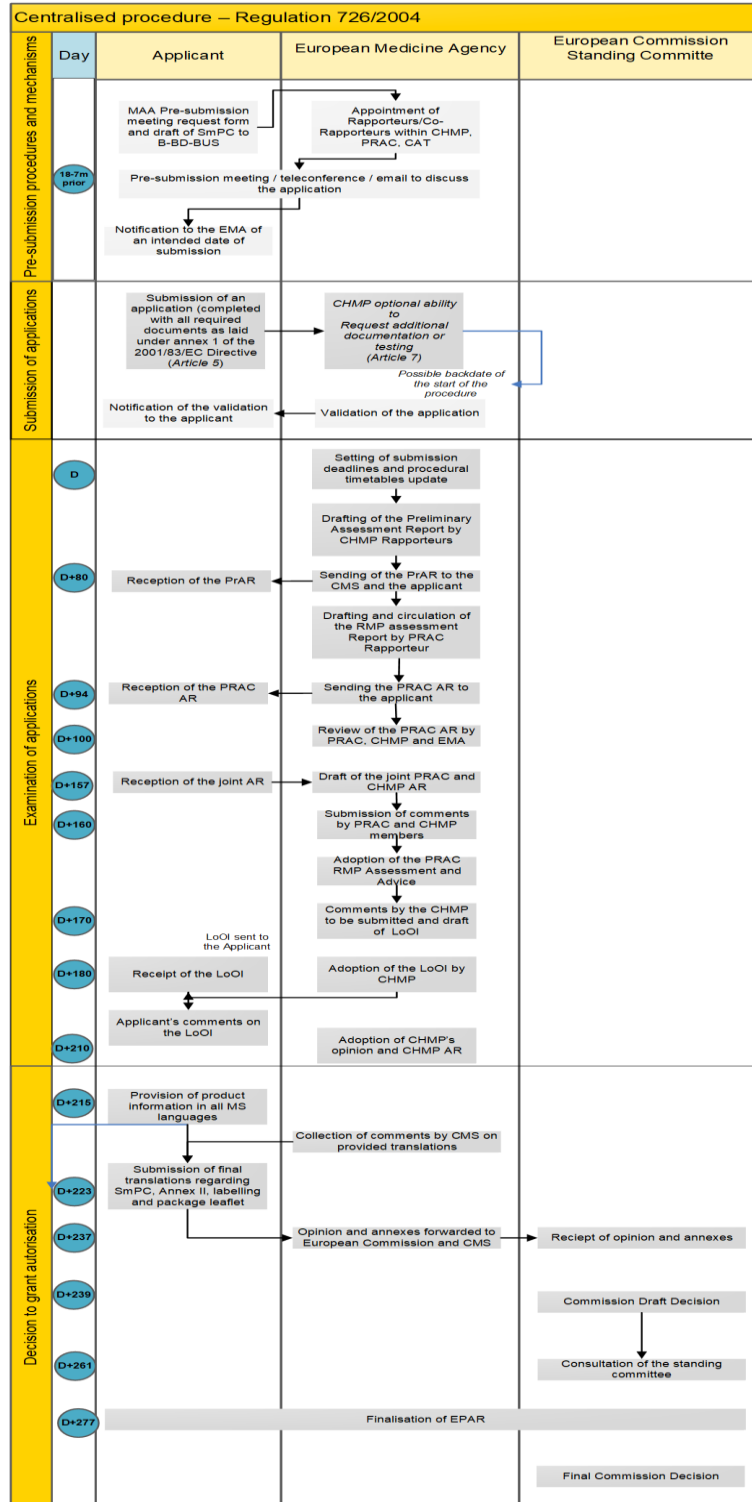
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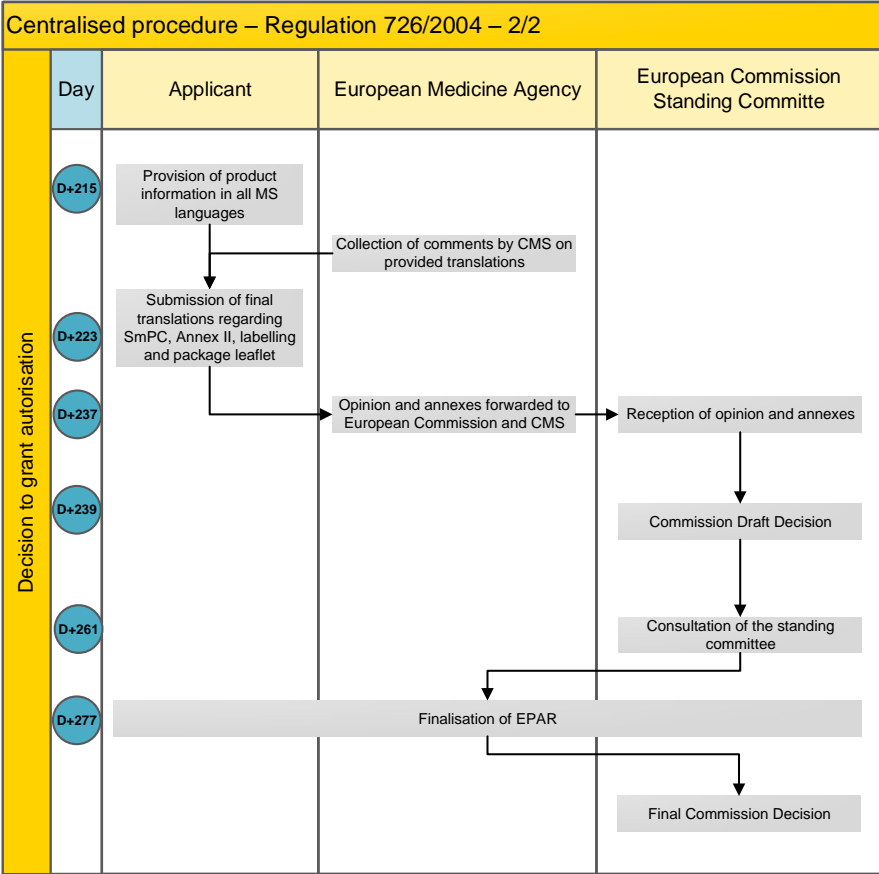
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# 10. Annexes

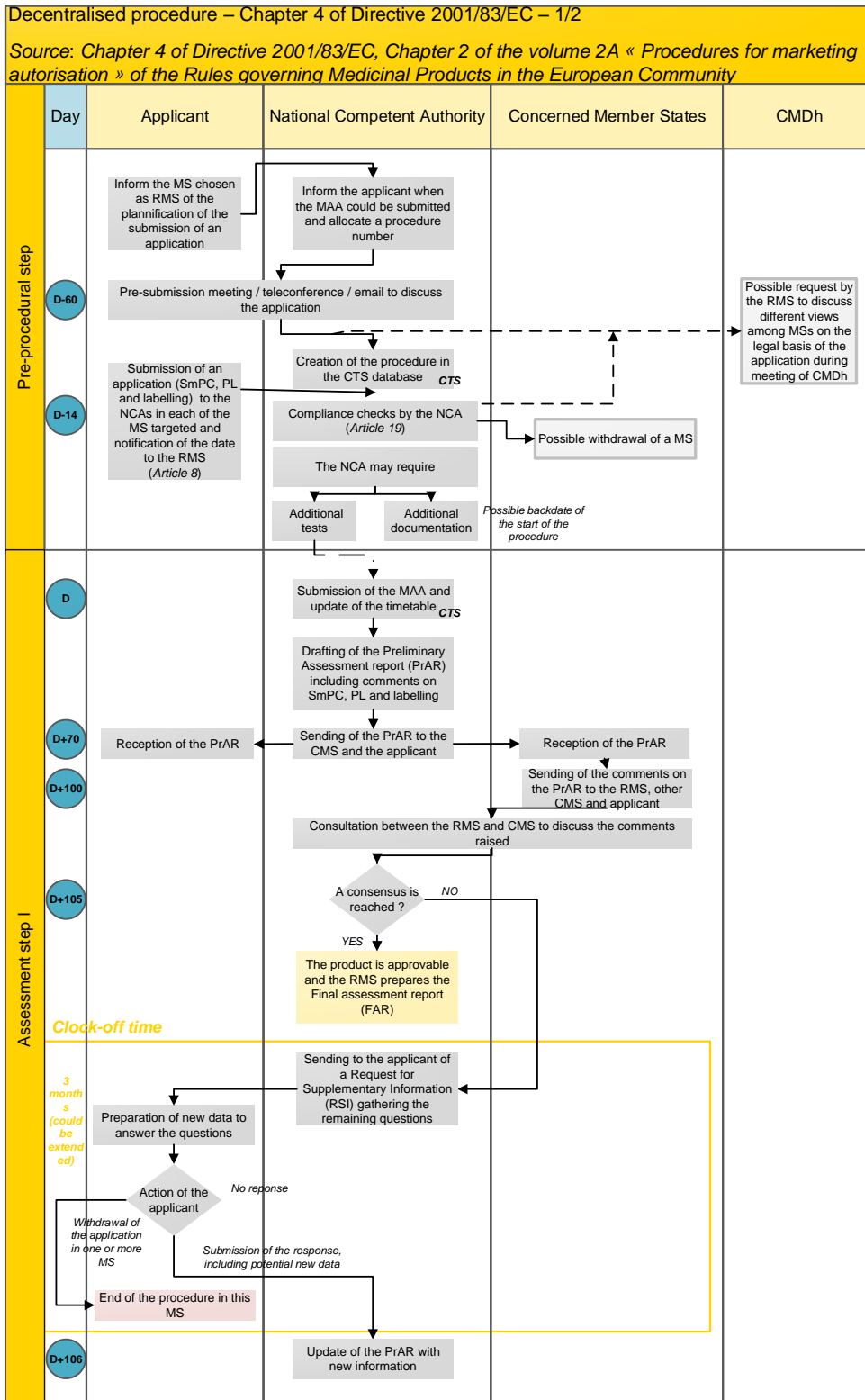
## 10.1. Mapping of Procedures

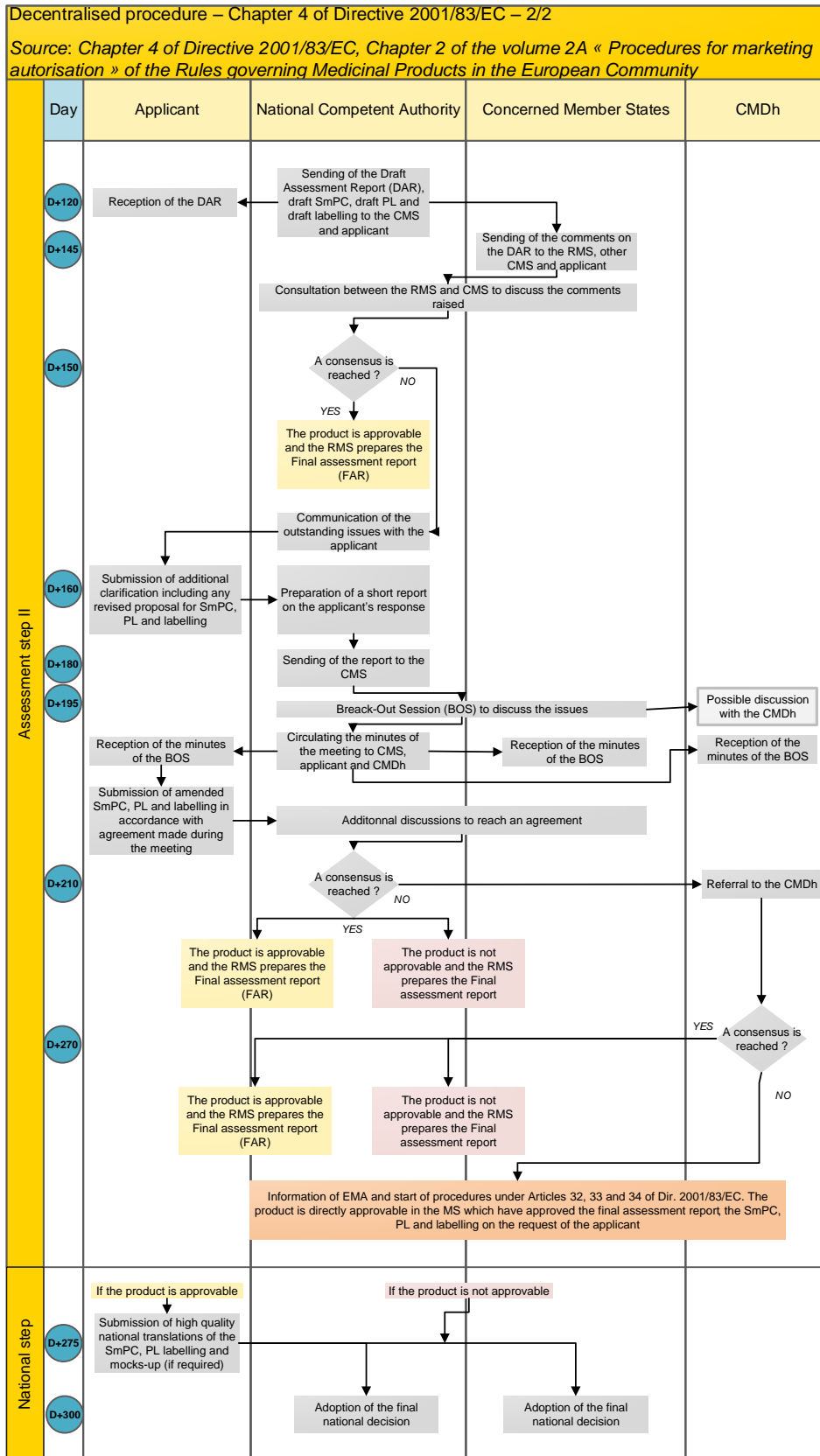
Figure 96 Centralised Procedure



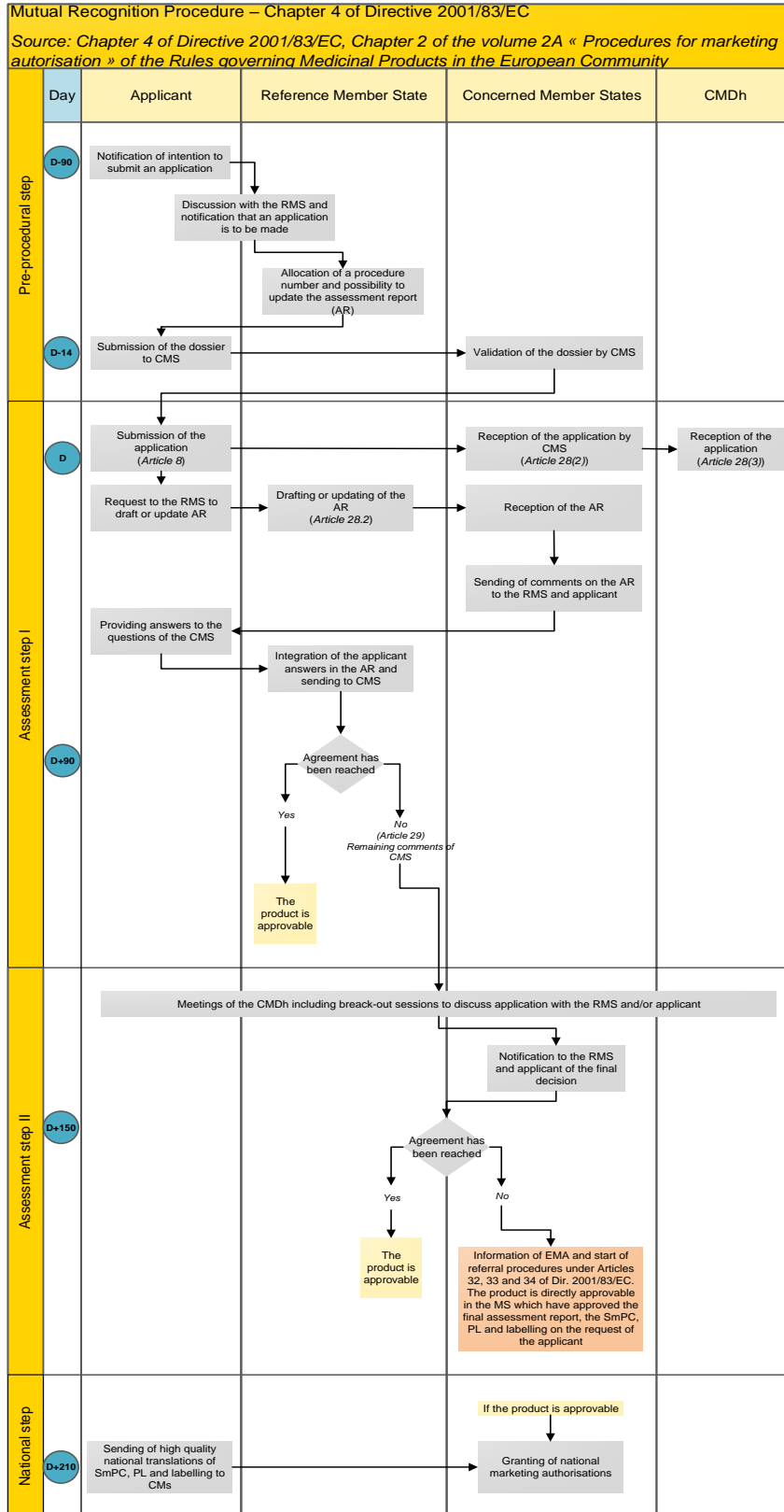


**Figure 97 Decentralised Procedure**





**Figure 98 Mutual Recognition Procedure**





## 10.2. List of Working Parties

### Standing Working Parties

Table 13: Standing Working Parties

Working Party Name	Initialism	Specific RoP	Year established	Meetings per year	Workplan		
					Publicly available	Year	Meetings
Biologics Working Party	BWP	Yes	2004	up to 11	No		
Healthcare Professionals' Working Party	HCPWP	Yes	2013	decided annually	Yes	2018 / 2019	3 / 4
Working Party on European Union Monographs and European Union List	HMPC-MLWP	Yes	2005	min 6	Yes	2018	6
Patients' and Consumers' Working Party	PCWP	Yes	2006	4±1	Yes	2018 / 2019	3 / 4
Quality Working Party	QWP	Yes		decided annually	Yes	2018	3
Scientific Advice Working Party	SAWP	Yes	2004	11	Yes	2018 / 2019	11 / 11
Safety Working Party	SWP	Yes	2004	max 11	No		

Source: EY

### Temporary Working Parties

Table 14: Temporary Working Parties

Working Party Name	Initialism	Specific RoP	Year established	Meetings per year	Workplan		
					Publicly available	Year	Meetings
Biosimilar Medicinal Products Working Party	BMWP	No		max 3	Yes	2018	2
Biostatistics Working Party	BSWP	No		max 3	Yes	2018	2 + 11 virtual
Blood Products Working Party	BPWP	No		max 3	Yes	2018	2 + 2 virtual
Cardiovascular Working Party	CVSWP	No		max 3	Yes	2018	2 + 3 virtual
Central Nervous System Working Party	CNSWP	No		max 3	Yes	2018	2
Infectious Diseases	IDWP	No		max 3	Yes	2018	2

Working Party							
Oncology Working Party	ONCWP	No		max 3	Yes	2018	2 + 11 virtual
Pharmacogenomics Working Party	PGWP	Yes	2009	max 5	Yes	2018	2
Pharmacokinetics Working Party	PKWP	No		max 3	Yes	2018	2
Rheumatology/Immunology Working Party	RIWP	No		max 3	Yes	2018	2
Vaccines Working Party	VWP	No		max 3	Yes	2018	2
Modelling and Simulation Working Party	MSWP	No	2013	max 3	Yes	2018	1 + 10 virtual
Formulation Working Group	FWG	No	2008		No		
Non-clinical Working Group	NcWG	No	2008		No		

Source: EY

## Drafting Groups

Table 15: Drafting Groups

Working Party Name	Initialism	Specific RoP	Year established	Meetings per year	Workplan		
					Publicly available	Year	Meetings
Excipients Drafting Group	ExcpDG	Yes	2015	max 3	Yes	2018	1 + 5 virtual
Gastroenterology Drafting Group		No		max 3	Yes	2018	2
Radiopharmaceuticals Drafting Group		No		max 3	Yes	2018	1 + 5 virtual
Respiratory Drafting Group	RDG	No		max 3	Yes	2018	2
Organisational Matters Drafting Group	DG ORGAM	No	2004	max 2	Yes	2018	1 + 6 virtual
Quality Drafting Group	Q DG	No	2004	max 2	Yes	2018	1 + 5 virtual

Source: EY

## Scientific Advisory Groups

Table 16: Scientific Advisory Groups

Working Party	Initialism	Specific	Year	Meetings	Workplan
---------------	------------	----------	------	----------	----------

Name		RoP	established	per year	Publicly available	Year	Meetings
Scientific Advisory Group on Cardiovascular Issues	SAG-CVS	No		on request	No		
Scientific Advisory Group on Anti-infectives	SAG-AI	No		on request	No		
Scientific Advisory Group on Diabetes / Endocrinology	SAG-D/E	No		on request	No		
Scientific Advisory Group on HIV / Viral Diseases	SAG-HIV/VD	No		on request	No		
Scientific Advisory Group on Neurology	SAG-N	No		on request	No		
Inter-Committee Scientific Advisory Group on Oncology	IC-SAG	Yes	2014	on request	No		
Scientific Advisory Group on Psychiatry	SAG-P	No		on request	No		
Scientific Advisory Group on Vaccines	SAG-V	No		on request	No		

Source: EY

## Other

Table 17: Other Groups

Working Party Name	Initialism	Specific RoP	Year established	Meetings per year	Workplan		
					Publicly available	Year	Meetings
(Invented) Name Review Group	NRG	Yes	2014	max 6	No		
Working Group on Quality Review of Documents	QRD	Yes	2014	max 4	Yes	2019	1 + 1 virtual
Expert Group on the Application of the 3Rs in the Development of Medicinal Products	J3RsWG	Yes	2013	1	Yes	2018	1
Active Substance Master File Working Group	ASMF WG	Yes	2011	next to CMDh / CHMP	No		
Geriatric Expert Group	GEG	Yes	2013	0	No		
Summary of Product Characteristics	SmPC AG	Yes	2009	0	Yes	2009	

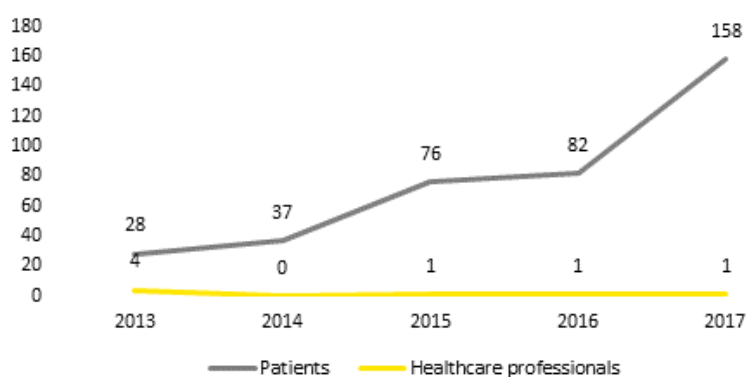
Advisory Group							
Guidelines Consistency Group	GCG	Yes	2010	0	No		
European Medicines Agency / CAT and Medical Devices' Notified Body Collaboration Group		Yes	2010	max 3	Yes	2011	

Source: EY

### 10.3. Patient and HCP involvement by activity

Patients and HCP were involved in a number of different EMA activities, namely: Scientific advice/protocol assistances; SAGs/ad-hoc expert meeting; Scientific committee/Working party consultations; workshops, Working Groups and other Ad-hoc activities; Membership of the Management Board, Committees and Working Parties and Documentary Review. The evolution of activity within each of these areas is presented below.

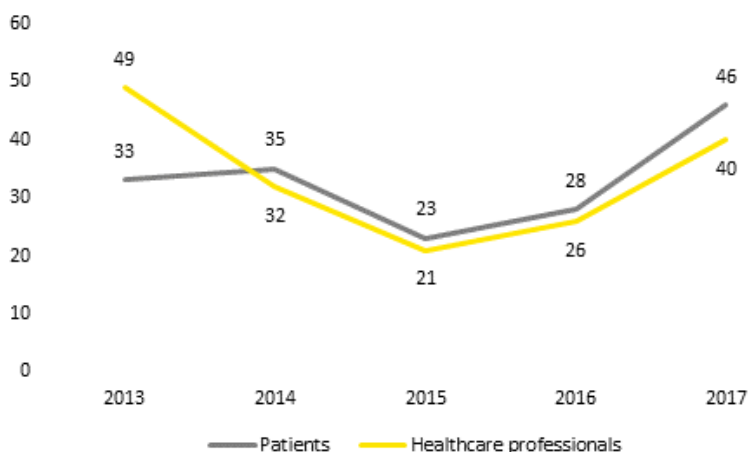
**Figure 99: Patient and HCP involvement – Scientific advice/protocol assistance<sup>141</sup>**



There has been a large increase in patient involvement in scientific advice activities. At the same time, HCP involvement remains an exception. Involvement in SAGs and ad-hoc expert meetings has experienced a short period of decline since 2013 but has since returned to the same levels.

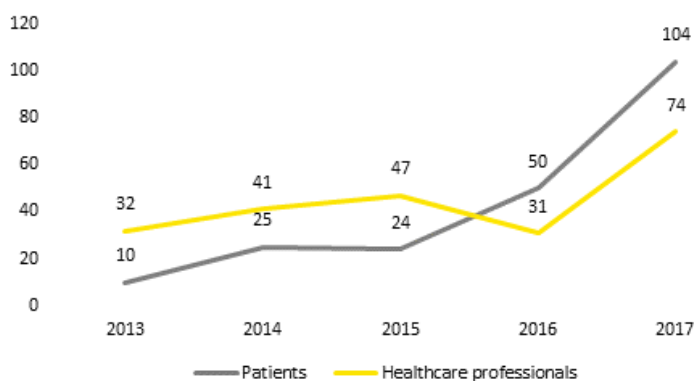
<sup>141</sup> EMA, Stakeholder Engagement Report 2017

**Figure 100: Patient and HCP involvement – SAGs/ad-hoc expert meetings<sup>142</sup>**



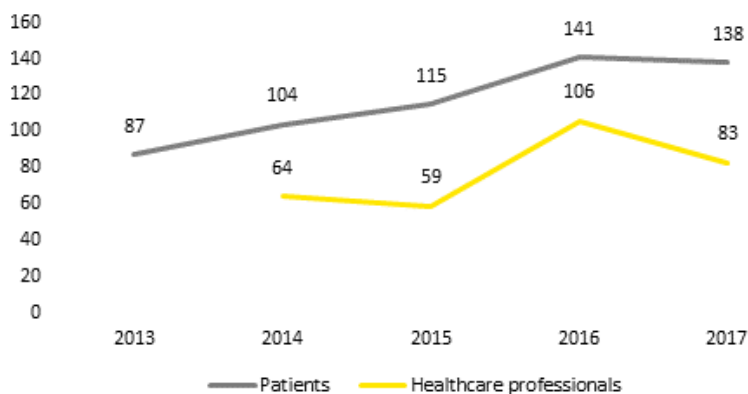
Scientific Committee and Working Party consultations have increased significantly both for patients and HCPs.

**Figure 101: Patient and HCP involvement – Scientific committee/working party consultations<sup>143</sup>**



Participation in workshops has steadily increased for patients from 87 in 2013 to 138 in 2017, with a smaller increase for HCPs from 64 in 2014 to 83 in 2017.

**Figure 102: Patient and HCP involvement – Workshops<sup>144</sup>**



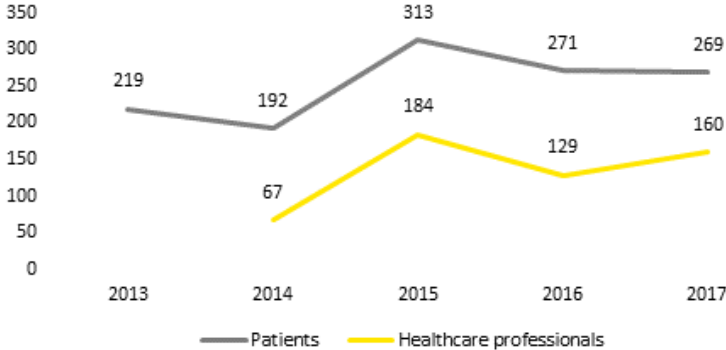
<sup>142</sup> EMA, Stakeholder Engagement Report 2017

<sup>143</sup> EMA, Stakeholder Engagement Report 2017

<sup>144</sup> EMA, Stakeholder Engagement Report 2017

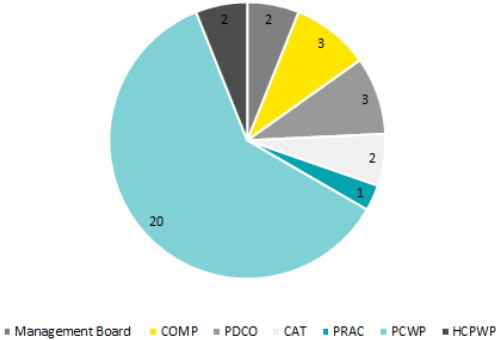
Participation in working groups and other ad hoc activities has fluctuated for both patients and HCPs, however overall numbers are relatively high, with patients participating in 269 working group and other ad-hoc activities in 2017 and HCPs participating in 160.

**Figure 103: Patient and HCP involvement – Working groups and other ad hoc activities<sup>145</sup>**



Membership by patients and HCP in the Management Board, Committees and Working Parties has slightly increased over the past years, with membership distributed in the following manner for patients.

**Figure 104: Patient Membership, 2017<sup>146</sup>**

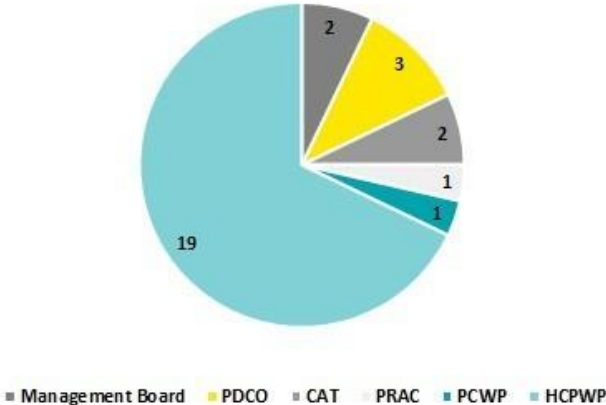


For HCPs, involvement in 2017 focussed on the Management Board and five committees and working parties.

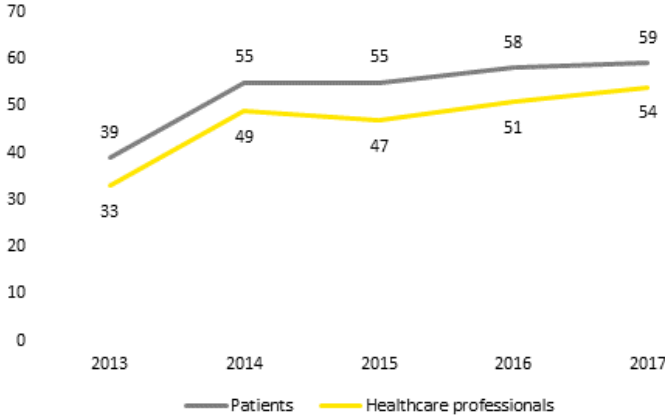
<sup>145</sup> EMA, Stakeholder Engagement Report 2017

<sup>146</sup> EMA, Stakeholder Engagement Report 2017

**Figure 105: HCP Membership, 2017<sup>147</sup>**



**Figure 106: Patient and HCP involvement – Membership in MB, committees, working parties<sup>148</sup>**



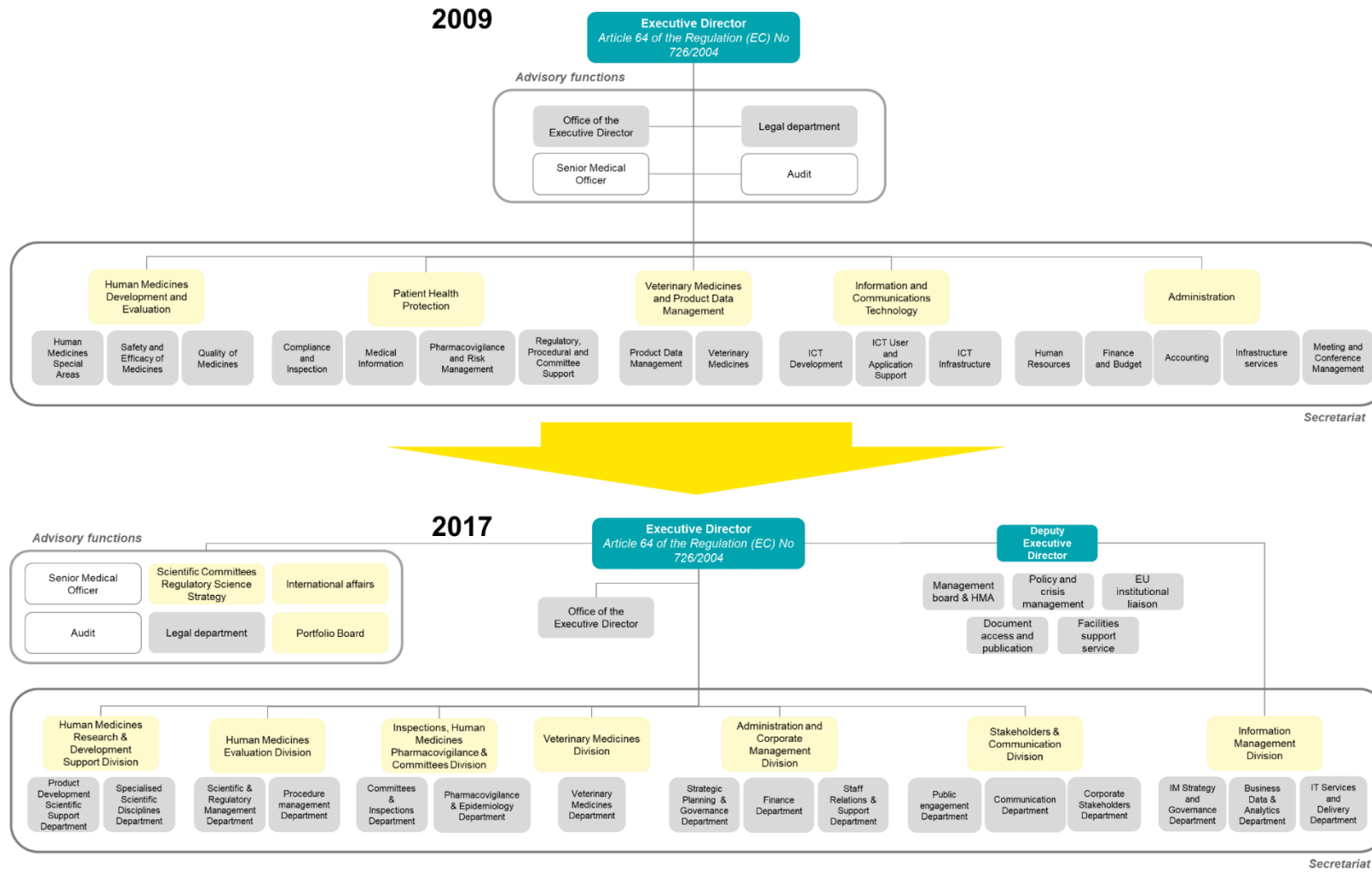
<sup>147</sup> EMA, Stakeholder Engagement Report 2017

<sup>148</sup> EMA, Stakeholder Engagement Report 2017



## 10.4. Evolution of the EMA organisation

Figure 107: Evolution of EMA organisation



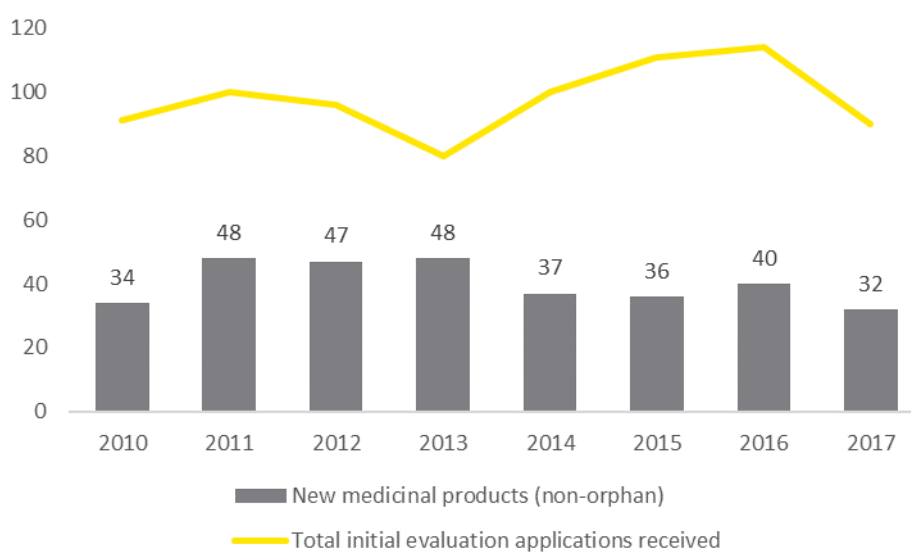
## 10.5. Marketing Authorisation Application Statistics

### The Centralised Procedure (CP)

When presenting initial evaluation applications received in the CP, EMA annual reports distinguish by different types.

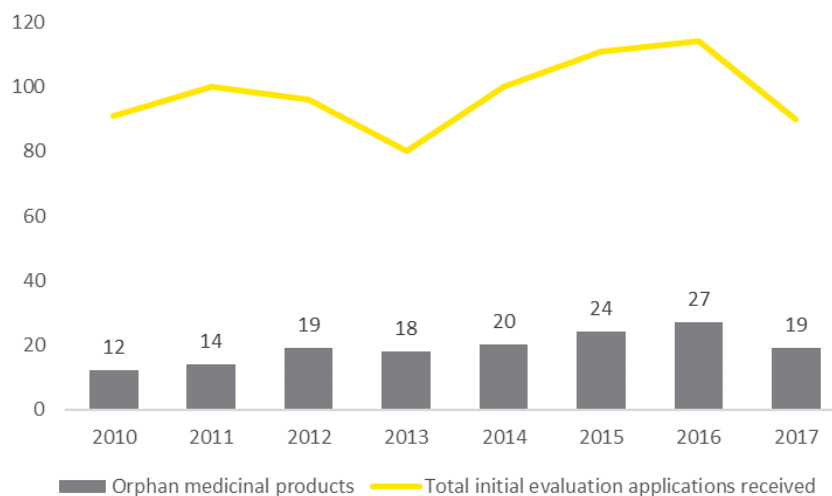
- ▶ **New medicinal products (non-orphan):** New medicines not falling under the subsequent categories
- ▶ **Orphan medicinal products (excl. ATMPs):** Medicines for rare diseases (except ATMP)
- ▶ **Generics, hybrid, informed consent-applications:** A medicine developed to be the same or similar (with the same active substance) as a medicine that has already been authorised
- ▶ **Biosimilars:** A biological medicine highly similar to another already approved biological medicine
- ▶ **ATMPs (orphan and non-orphan):** A medicine based on genes, cells or tissue engineering
- ▶ **Paediatric use marketing authorisations:** Medicines developed exclusively for use in children
- ▶ **Scientific opinions for non-EU markets:** Medicine used exclusively outside the EU

Figure 108: Initial evaluation applications received – New medicinal products<sup>149</sup>

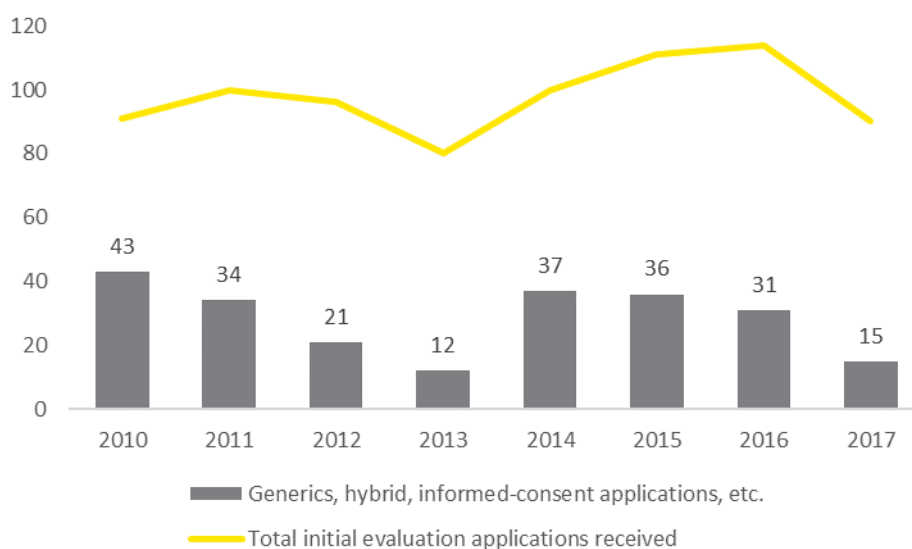


<sup>149</sup> EMA, Annual Reports, 2010-2017

**Figure 109: Initial evaluation applications received – Orphan medicinal products<sup>150</sup>**



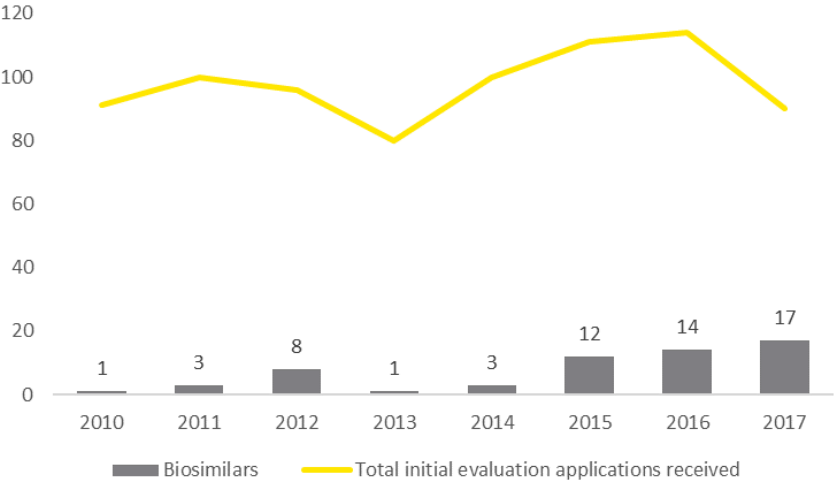
**Figure 110: Initial evaluation applications received – Generics, hybrid, informed-consent applications etc.<sup>151</sup>**



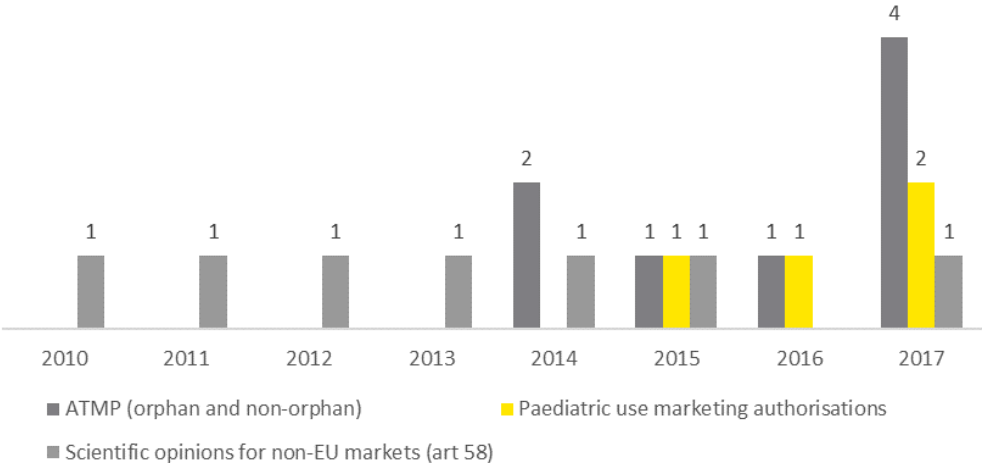
<sup>150</sup> EMA, Annual Reports, 2010-2017

<sup>151</sup> EMA, Annual Reports, 2010-2017

**Figure 111: Initial-evaluation applications received – Biosimilars<sup>152</sup>**



**Figure 112: Initial-evaluation applications received – ATMP (orphan and non-orphan), Paediatric use marketing authorisations and scientific opinions for non-EU markets (Article 58)<sup>153</sup>**

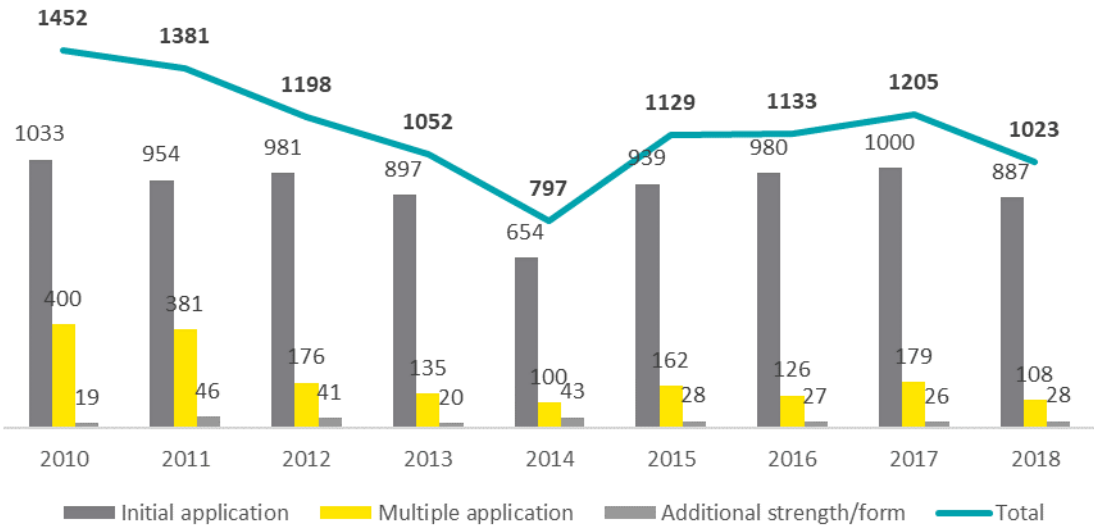


<sup>152</sup> EMA, Annual Reports, 2010-2017

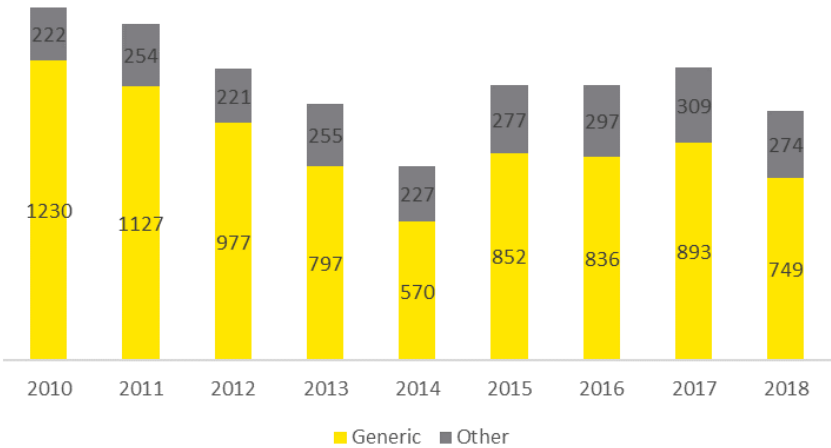
<sup>153</sup> EMA, Annual Reports, 2010-2017

**The Decentralised Procedure (DCP)**

**Figure 113: DCP per type of procedure<sup>154</sup>**



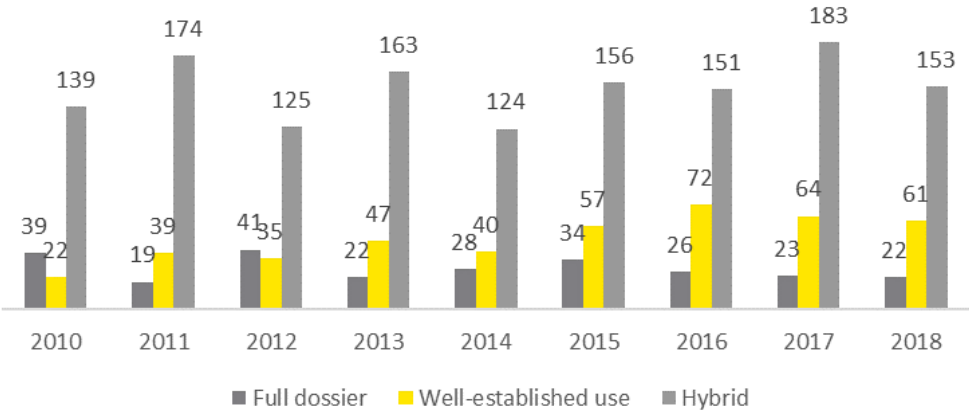
**Figure 114: DCP per legal basis (1/3)<sup>155</sup>**



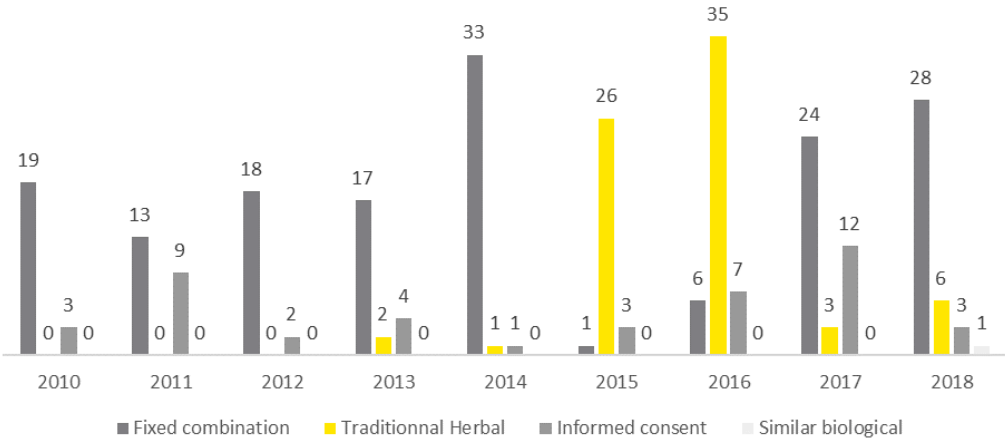
<sup>154</sup> HMA, Annual Statistics 2010-2018

<sup>155</sup> HMA, Annual Statistics 2010-2018

**Figure 115: DCP per legal basis (2/3)<sup>156</sup>**



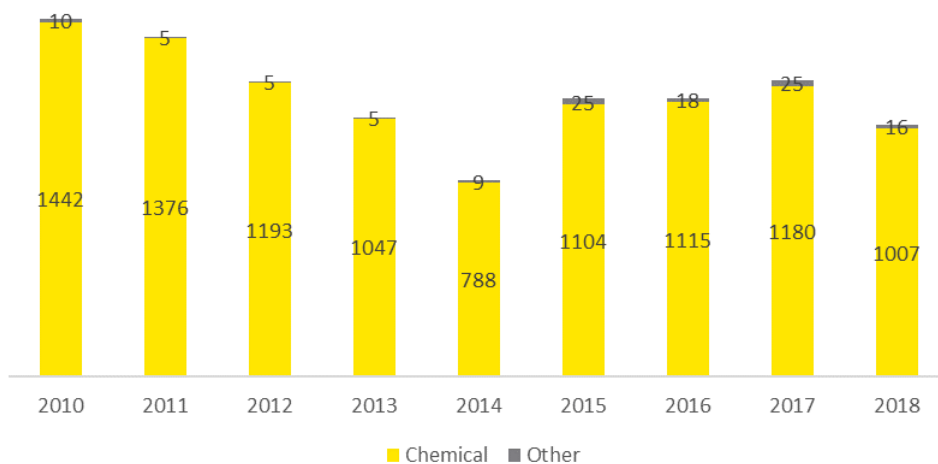
**Figure 116: DCP per legal basis (3/3)<sup>157</sup>**



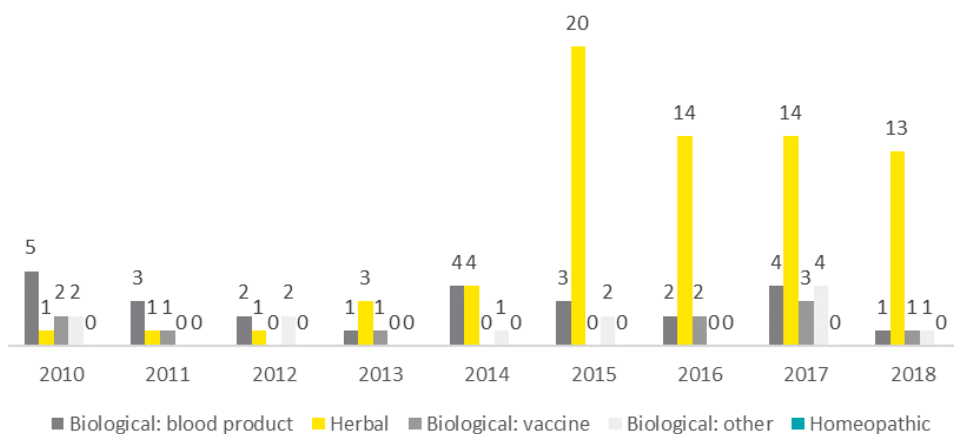
<sup>156</sup> HMA, Annual Statistics 2010-2018

<sup>157</sup> HMA, Annual Statistics 2010-2018

**Figure 117: DCP per type of product (1/2)<sup>158</sup>**



**Figure 118: DCP per type of product (2/2)<sup>159</sup>**

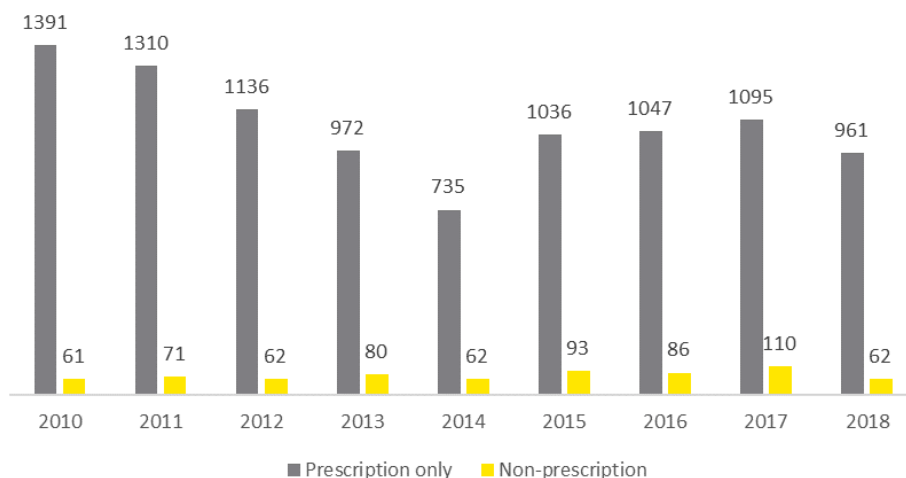


<sup>158</sup> HMA, Annual Statistics 2010-2018

<sup>159</sup> HMA, Annual Statistics 2010-2018

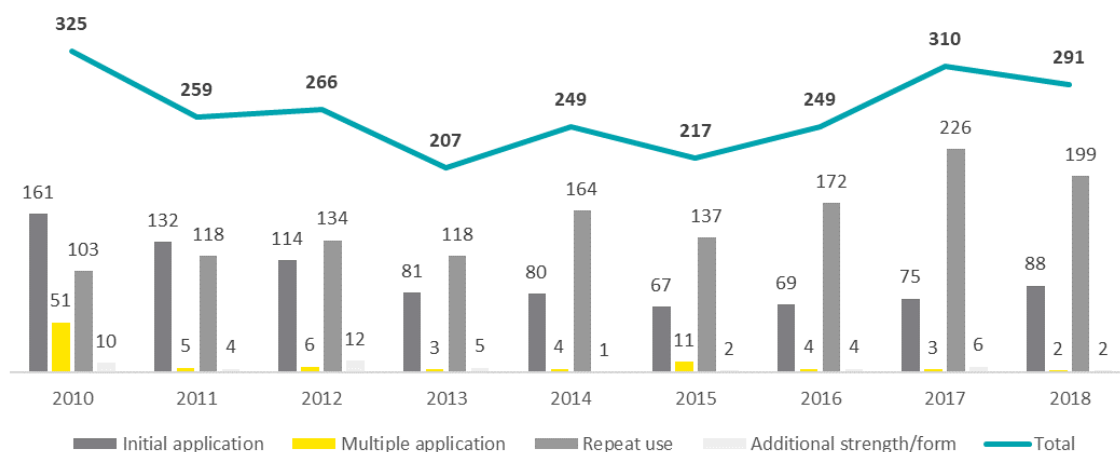


**Figure 119: DCP per prescription status**<sup>160</sup>



**The Mutual Recognition Procedure (MRP)**

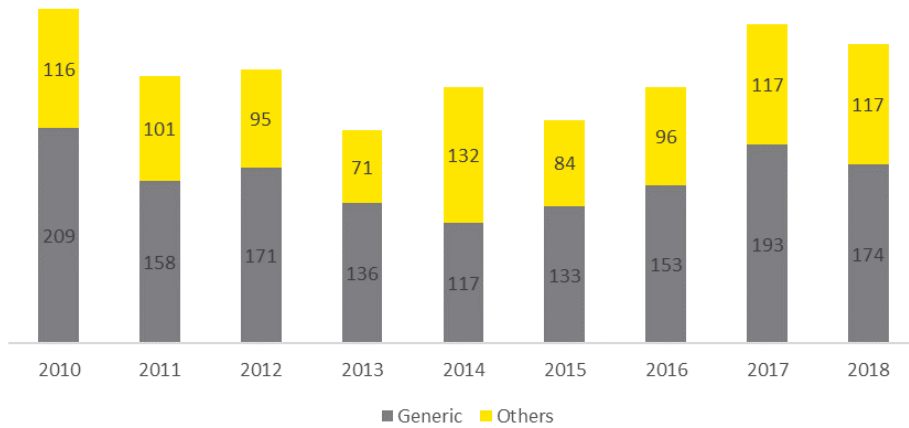
**Figure 120: MRP per type of procedure**<sup>161</sup>



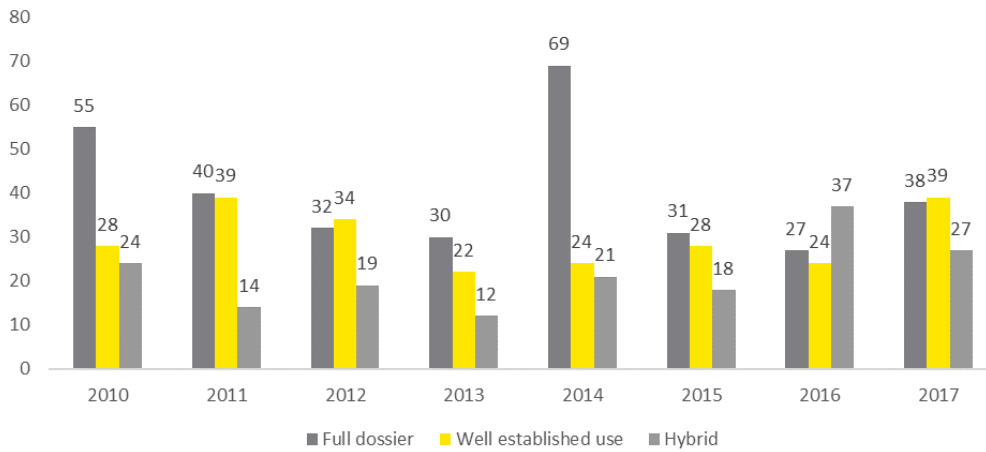
<sup>160</sup> HMA, Annual Statistics 2010-2018

<sup>161</sup> HMA, Annual Statistics 2010-2018

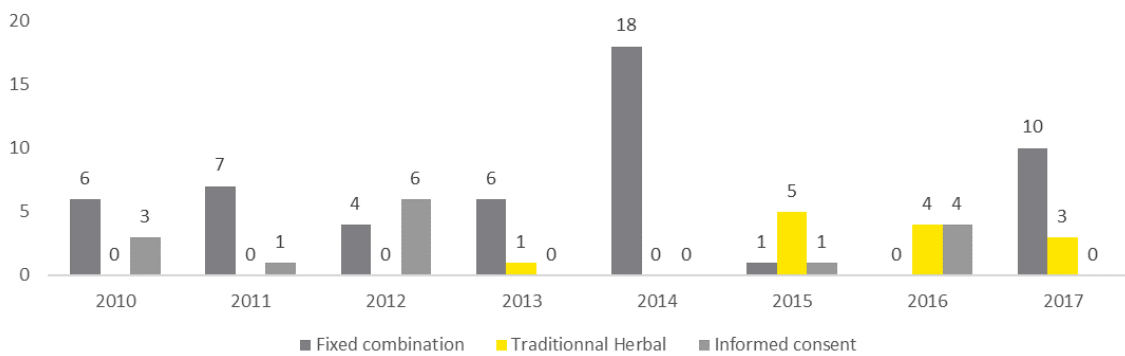
**Figure 121: MRP per legal basis (1/3)**<sup>162</sup>



**Figure 122: MRP per legal basis (2/3)**<sup>163</sup>



**Figure 123: MRP per legal basis (3/3)**<sup>164</sup>

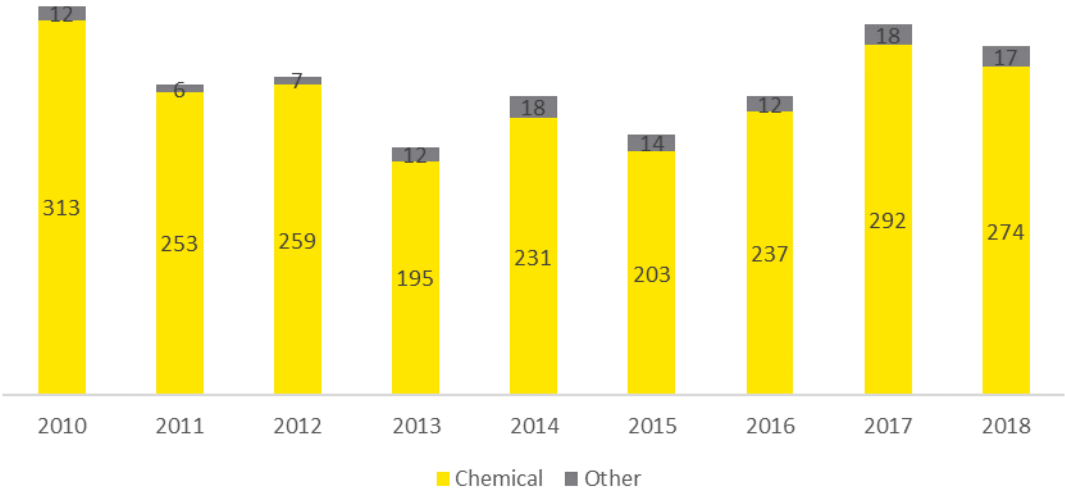


<sup>162</sup> HMA, Annual Statistics 2010-2018

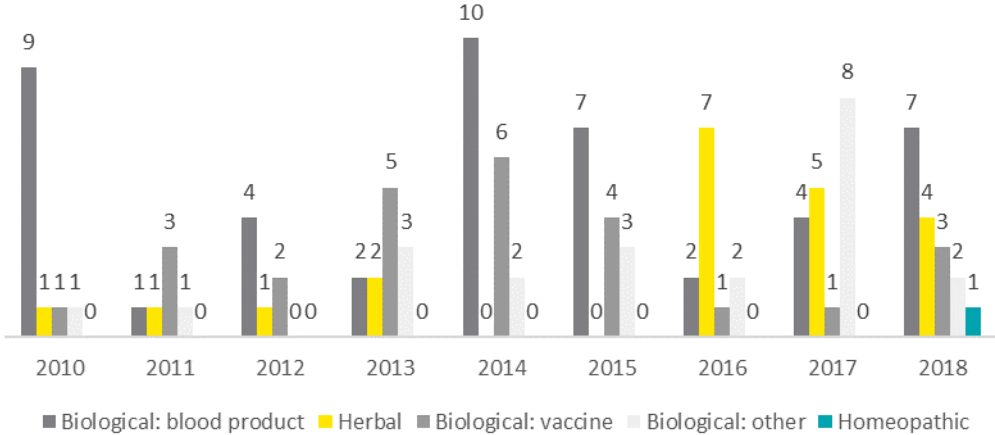
<sup>163</sup> HMA, Annual Statistics 2010-2018

<sup>164</sup> HMA, Annual Statistics 2010-2018

**Figure 124: MRP per type of product (1/2)<sup>165</sup>**



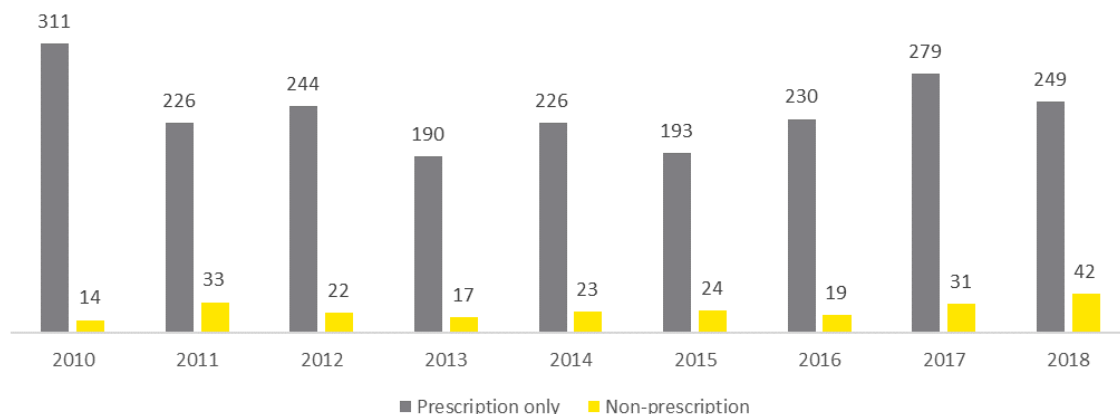
**Figure 125: MRP per type of product (2/2)<sup>166</sup>**



<sup>165</sup> HMA, Annual Statistics 2010-2018

<sup>166</sup> HMA, Annual Statistics 2010-2018

**Figure 126: MRP per prescription status<sup>167</sup>**



## 10.6. EMA Telematics

### Box 8: EMA telematics

Article 57 Database:	This is the database on all medicines authorised in the European Economic Area (EEA). The submission of the information is a legal requirement and must be kept up to date.
CESP:	The Common European Submission Portal (CESP) is a mechanism of exchange between applicants and regulatory agencies, allowing for secure communication and central submission of applications.
Common Repository:	The Common Repository allows all NCAs to search, browse and download Centralised Procedure submission for human products. It acts as an electronic filing area to hold dossiers submitted electronically.
CTS:	The Communication and Tracking System (CTS) is used to support coordination and tracking of marketing authorities by the NCAs in the DCP/MRP procedures.
eAF:	The electronic Application Form (eAF) has replaced the analogue application form and allows for electronic data import and other digital tools to be used within the form.
eSubmission Gateway & Portal:	The eSubmission Gateway and Portal are electronic submission channels that allow applicants to submit all types of human and veterinary applications securely over the internet. The web-based portal is specifically aimed at SMEs. The use of these channels is mandatory for all applications.
EU Veterinary (V) Product Database:	This database is a source of information on all medicinal products for veterinary use that have been

<sup>167</sup> HMA, Annual Statistics 2010-2018

	authorised in the EEA.
EudraCT:	The European Clinical Trials Database (EudraCT) is the system for the registration of clinical trials. It is currently undergoing an update through which summary clinical trial results will be made publicly available.
EudraCT Data Warehouse (DW):	This data warehouse is a collection of information on the Clinical Trails registered through the EudraCT system.
EudraGMDP:	EudraGMDP is a database containing information on manufacturing and import authorisations, Good Manufacturing Practice (GMP) certificates, statements of non-compliance with GMP and CMP inspection planning in third countries.
EudraNet, including EudraLink, EudraMail, Eudra Common Directory:	<p>EudraNet is a secure network which acts as the backbone of the EMA Regulatory Systems. It facilitates secure communication and enables access to applications hosted at the EMA.</p> <p>Eudralink refers to the system in EudraNet to send files securely over the internet.</p> <p>EudraMail is the systems email service, used to communicate securely between Members of the EMA network.</p> <p>The Eudra Common Directory is the directory in which users must be registered in order to access the various Eudra Telematics</p>
EudraPharm Human (H):	EudraPharm is a source of information on human medicines authorised in the EEA, containing information provided by both NCAs and the EMA.
EudraVigilance H and DW H, EudraVigilance V and DW V:	Eudravigilance is a pharmacovigilance system that is currently being implemented. It facilitates the electronic exchange of individual safety reports, early detection and evaluation of signals as well as product information. It includes an automated safety and message-processing system and a large pharmacovigilance database.
EUTCT:	The European Union Telematics Controlled Terms (EUTCT) System is a provider of lists of Substances in multiple languages for the ongoing exchange of data between member throughout the EMA Regulatory Network (EMRN)
Organisation Management Services:	The Organisation Management Services (OMS) provides a single source of validated organisation data that can be used as a reference to support EU regulatory activities and business processes. It stores master data such as organisation name and address for organisations such as marketing authorisation holders, sponsors, regulatory authorities and manufacturers.
PSUR Repository:	The PSUR repository is a single, central platform for PSURs and related documents to be used by all regulatory authorities and pharmaceutical companies in the EU. It allows stakeholders to send

Referential Management Services:	all PSURs and related submissions to a single recipient. The Referential Management Services (RMS) stores referential master data, i.e. lists of terms (controlled vocabularies) to describe the attributes of medicinal products, such as lists of dosage forms, units of measurement and routes of administration.
SIAMED Dashboard:	SIAMED is an international system developed by the WHO for Computer-Assisted Drug Registration. It allows regulatory authorities access to information on marketing authorisations

## 10.7. Overview of Data Collection

### 10.7.1. Interviews

A number of interviews were conducted with stakeholders at EU and international level. A total of 20 interviews were conducted. The sub-sections below present the details of the interviews that were conducted successfully as well as those stakeholders that the study team was not able to reach.

#### Interviews with EMA

Interviews were organised with the EMA Secretariat in London on 5 and 6 November 2018, with four team members from the Study Team attending these interviews over the course of two days.

In order to ensure that all the necessary staff from the Secretariat were included in the interviews, the EMA Secretariat organised grouped interviews per Work Package, with up to five persons participating in these interviews.

The interviews with the EMA Secretariat permitted the Study Team to discuss issues under all five Work Packages. Through discussions, the Study Team identified pertinent documentation to include in the desk research and other pertinent data. This was the case, for example, in relation to Work Package 5 relating to communication activities, where the Study Team was provided with considerable documentation on the activities undertaken by the EMA Secretariat as well as surveys previously undertaken to stakeholders on their communication activities.

These interviews also enabled the Study Team to understand issues which may not have been identified through initial desk research.

**Table 18 Overview of interviews undertaken and key points of discussion**

Work Package	Participants
<b>WP1 – The European Medicines Regulatory Framework:</b>	<ul style="list-style-type: none"> <li>▶ <b>Nerimantas Steikunas</b>, Head of Administration and Corporate Management Division</li> <li>▶ <b>Anthony Humphreys</b>, Head of Scientific Committees Regulatory Science Strategy</li> <li>▶ <b>Michael Lenihan</b>, Head of Strategic Planning and Governance Department</li> <li>▶ <b>Silvia Fabiani</b>, Head of Management Board and HMA Office</li> <li>▶ <b>Hilde Boone</b>, Head of EU Institutional Liaison Office</li> </ul>
<b>WP2 – Procedures preceding the submission of MMAs:</b>	<ul style="list-style-type: none"> <li>▶ <b>Enrica Alteri</b>, Head of Human Medicines Research and Development Support Division</li> <li>▶ <b>Michael Berntgen</b>, Head of Product Development Scientific Support Department</li> <li>▶ <b>Jordi Llinares Garcia</b>, Head of Scientific and Regulatory Management Department</li> <li>▶ <b>Spiros Vamvakas</b>, Head of Scientific Advice Office</li> </ul>
<b>WP3 – Initial</b>	<ul style="list-style-type: none"> <li>▶ <b>Zaide Frias</b>, Head of Human Medicines Evaluation Division</li> </ul>

<b>marketing authorisation procedures</b>	<ul style="list-style-type: none"> <li>▶ <b>Evdokia Korakianiti</b>, Head of Procedure Management Department</li> <li>▶ <b>Jordi Llinares Garcia</b>, Head of Scientific and Regulatory Management Department</li> <li>▶ <b>Sonia Ribeiro</b>, Head of Regulatory Affairs Office</li> </ul>
<b>WP4 – Post marketing authorisation procedures</b>	<ul style="list-style-type: none"> <li>▶ <b>Fergus Sweeney</b>, Head of Inspections, Human Medicines Pharmacovigilance and Committees Division</li> <li>▶ <b>Zaide Frias</b>, Head of Human Medicines Evaluation Division</li> <li>▶ <b>Anabela de Lima Marçal</b>, Head of Committees and Inspections Department</li> <li>▶ <b>Peter Arlett</b>, Head of Pharmacovigilance and Epidemiology Department</li> <li>▶ <b>Sonia Ribeiro</b>, Head of Regulatory Affairs Office</li> </ul>
<b>WP5 – Support activities</b>	<ul style="list-style-type: none"> <li>▶ <b>Melanie Carr</b>, Head of Stakeholders and Communication Division</li> <li>▶ <b>Alexis Nolte</b>, Head of Information Management Division</li> <li>▶ <b>Marie-Agnes Heine</b>, Head of Communication Department</li> <li>▶ <b>Juan Garcia Burgos</b>, Head of Public Engagement Department</li> <li>▶ <b>Sarah Weatherley</b>, Head of Telematics and Governance Office</li> </ul>

### Interviews with the European Commission

Interviews were conducted on site in Brussels on 22 October 2018 at DG SANTE.

Nine face-to-face interviews were conducted with members of DG SANTE and the legal service.

- ▶ Kaja Kantorska (COMP)
- ▶ Martin Dorazil (MRP – DCP/DMP)
- ▶ Attila Sipos (Legal services, DMP/Litigations)
- ▶ Marco Capellino (general EMRN/fees)
- ▶ Helen Lee
- ▶ Olga Salomon (Head of Unit)
- ▶ Dagmar Stara (CHMP)
- ▶ Aleksandra Opalska (PRAC)
- ▶ Rocio Salvador Roldan (ATMP)

In addition to the face-to-face interviews, a telephone interview was held with Ms Rocio Salvador-Roldan on 23 October 2018.

Interviews with DG SANTE permitted the study team to gain more in-depth knowledge about the procedures and collaboration with EMA and the internal procedures in place with the Commission. Moreover, products to be analysed during the product case studies were identified.

- ▶ In addition to the interviews undertaken with DG SANTE, an interview was conducted with Mr Carlo Petinelli of DG GROW

### Interviews with the European Parliament

One interview was conducted with a Member of the European Parliament. The other requests by the study team did not receive a response, despite a reminder being sent out.

**Table 19 Interviews with the European Parliament**

Stakeholder	Status
<b>Biljana Borzan</b> , Deputy Member of the European Parliament, EP-EMA Liaison points	Conducted – 30/01/2019
<b>Dagmar Roth Behrendt</b> , Ex vice president of the European Parliament (2009-	No response

2012, 2004-2007), EP-EMA Liaison points	
<b>Matthias Groote</b> , European Deputy (2005-2016), EP-EMA Liaison points	No response
<b>Adina Loana Valean</b> , Member of the European Parliament, ENVI Committee	No response
<b>Françoise Grossette</b> , Member of the European Parliament, ENVI Committee	No response

### Interviews with International Agencies

There is an outstanding interview with the FDA, the initial interview had to be postponed to due scheduling issues. The study team has not received a response from the JPMDA despite multiple reminders.

**Table 20 Interviews with International Agencies**

Stakeholder	Status
<b>FDA</b> – Ms Janet Woodcock (Director of the Center for Drug Evaluation and Research)	Postponed
<b>JPMDA</b> - Tatsuya Konda (Chief executive JPMDA)	No response

### Interviews with pharmaceutical industry umbrella organisations

Five pharmaceutical industry umbrella organisations were interviewed.

**Table 21 Interviews with pharmaceutical industry umbrella organisations**

Stakeholder	Status
EUCOPE	Completed – 06/12/2018
EFPIA	Completed – 31/01/2019
EIPG	No response
Medicines for Europe	Completed – 20/12/2018
APIC	No response
ECHAMP	Completed – 17/04/2019
AESGP	Completed – 26/02/2019

### Interviews with patient and consumer organisations

Three out of five initially planned patient and consumer organisations were interviewed.

**Table 22 Interviews with patient and consumer organisations**

Stakeholder	Status
EPF	No response
EPHA	Completed – 03/12/2018
BEUC	Completed – 05/12/2018
HAI	Completed – 22/11/2018
IAPO	No response



### Interviews with Healthcare organisations

One Healthcare organisation responded to the interview request.

**Table 23 Interviews with healthcare organisations**

Stakeholder	Status
EFIM	No response
CPME	No response
EFPC	No response
PGEU	Completed – 14/12/2018

### Interviews with international organisations

No international organisations targeted for this study have responded to the interview requests.

**Table 24 Progress of interviews with international organisations**

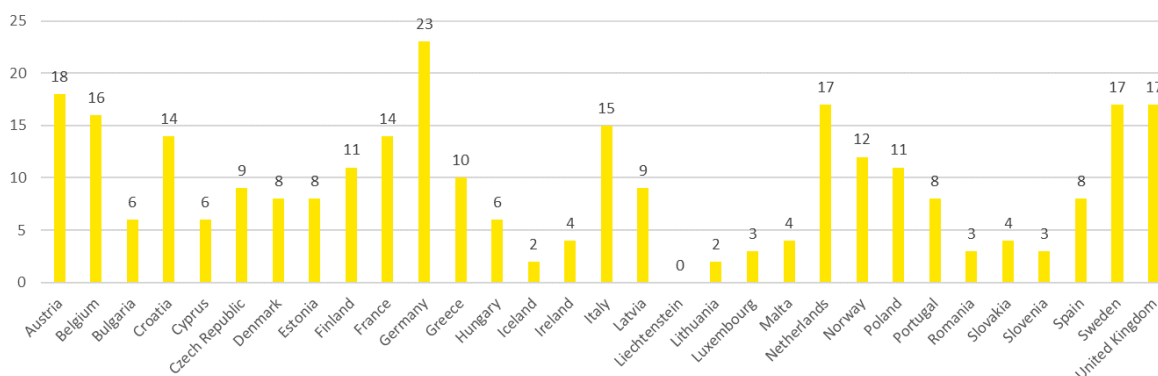
Stakeholder	Status
WHO	No response
Council of Europe	No response

#### 10.7.2. Online Survey

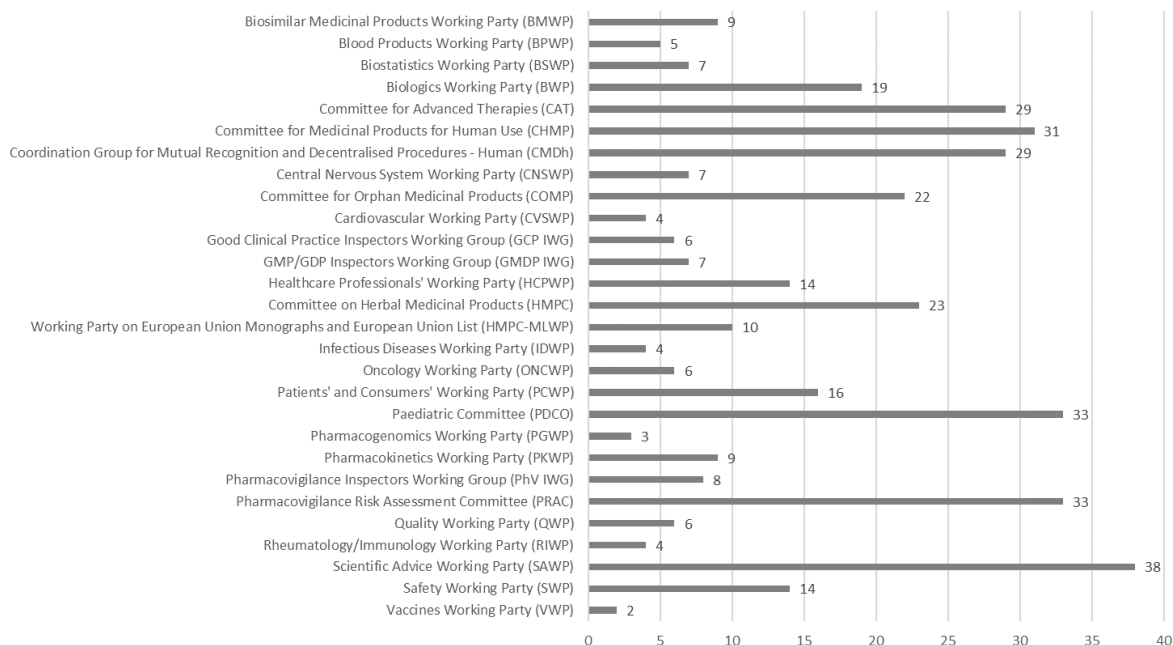
The online survey was sent out to 888 experts. In total, 288 experts responded. At least one expert from every country responded, with the exception of Liechtenstein. Furthermore, at least 2 experts responded from each of the targeted Committees and Working Parties. The two graphs below provide an overview of the profiles of the respondents.

The Online Survey questionnaire was composed of both closed and open questions with an opportunity for the respondents to provide their input to the study. The survey was launched through the EY Online Survey tool which enabled the study team to add different filters per question adapted to the different types of experts (e.g. committee experts, rapporteurs etc.) as well as permitted the study team to monitor the level of responses and launch survey reminders as necessary.

**Figure 127: Respondents by Country**



**Figure 128: Respondents by Committee / Working Party**



### 10.7.3. Written Questionnaires

The National Competent Authorities (NCAs) were consulted through a written questionnaire as well as in some cases through follow-up telephone interviews.

The questionnaire was sent to all 32 NCAs in the EMA network. This was done to quantify the perception of NCAs relating to several aspects of the effectiveness and efficiency of the procedures for authorization and monitoring of medicinal products. Depending on the responses to the questionnaire and upon specific request, the study team performed a telephone follow-up interview with NCAs in order to deepen our understanding of their perceptions provided in the questionnaire. Two of these interviews were conducted. The NCA questionnaire and interviews do not encompass the interviews conducted in the scope Member State Case Studies with the eight relevant NCAs.

22 NCAs returned a completed questionnaire, the table below provides an overview.

**Table 25: NCA responses**

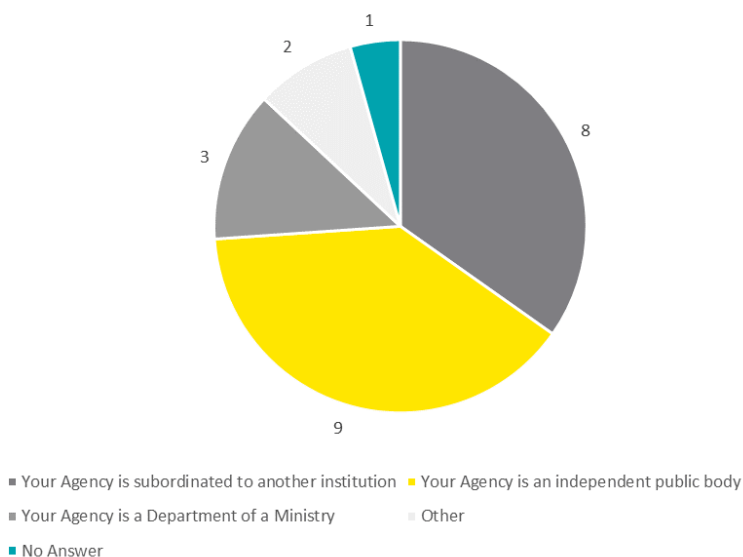
Member State NCA	Questionnaire status	Follow up Interview
<b>Austria - Austrian Agency for Health and Food Safety</b>	Completed	
<b>Belgium - Federal Agency for Medicines and Health Products</b>	Completed	
<b>Bulgaria - Bulgarian Drug Agency</b>	No response	
<b>Croatia - Agency for medicinal products and medical devices of Croatia</b>	Completed	
<b>Cyprus - Ministry of Health - Pharmaceutical Services</b>	No response	
<b>Czech Republic - State Institute for Drug Control</b>	Completed	
<b>Denmark - Danish Medicines Agency</b>	Completed	
<b>Estonia - State Agency of Medicines</b>	Completed	
<b>Finland - Finnish Medicines Agency</b>	Completed	
<b>France - National Agency for the Safety of Medicine and</b>	Completed	

<b>Health Products</b>		
<b>Germany - Federal Institute for Drugs and Medical Devices (BfArM)</b>	Completed	
<b>Germany - Paul Ehrlich Institute (PEI)</b>	Completed	
<b>Greece - National Organization for Medicines</b>	Completed	
<b>Hungary - National Institute of Pharmacy and Nutrition</b>	No response	
<b>Iceland - Icelandic Medicines Agency</b>	Completed	
<b>Ireland - Health Products Regulatory Authority (HPRA)</b>	Declined	
<b>Italy - Italian Medicines Agency</b>	Completed	
<b>Latvia - State Agency of Medicines</b>	Completed	
<b>Liechtenstein - Office of Health / Department of Pharmaceuticals</b>	Completed	
<b>Lithuania - State Medicines Control Agency</b>	Completed	
<b>Luxembourg - Ministry of Health</b>	No response	
<b>Malta - Medicines Authority</b>	No response	
<b>Netherlands - Medicines Evaluation Board</b>	Completed	
<b>Norway - Norwegian Medicines Agency</b>	Completed	
<b>Poland - Office for Registration of Medicinal Products, Medical Devices and Biocidal Products</b>	No response	
<b>Portugal - National Authority of Medicines and Health Products</b>	Completed	
<b>Romania - National Medicines Agency</b>	No response	
<b>Slovakia - State Institute for Drug Control</b>	No response	
<b>Slovenia - Agency for Medicinal Products and Medical Devices of the Republic of Slovenia</b>	Completed	
<b>Spain - Spanish Agency for Medicines and Health Products</b>	Completed	✓
<b>Sweden - Medical Products Agency</b>	Completed	✓
<b>United Kingdom - Medicines and Healthcare Products Regulatory Agency</b>	Completed	

Regarding the 22 National Competent Authorities who answered the questionnaires:

- ▶ 8 NCAs are subordinated to another institution
- ▶ 9 NCAs are an independent public body
- ▶ 3 are a Department of a Ministry
- ▶ 2 NCAs answered other
- ▶ 1 did not answer

**Figure 129: Types of NCAs responding to the questionnaire**



#### 10.7.4. Direct Observation

Direct Observations were undertaken in London of the three following committees, as foreseen in the Inception Report.

- ▶ CHMP – 17/20 September 2018
- ▶ PRAC – 1/4 October 2018
- ▶ CMDh – 17/19 September 2018 (including a presentation of the study)

The aim of these observations was to identify the manner in which the participants cooperate with each other and to assess the level of dialogue and interaction with a view to providing input to Work Package 1.

In addition to the Direct Observation with these committees, the EY team presented the aims and objectives of the study at the EMA Management Board on 4 October 2018. This enabled the study team to ensure that the Management Board members identified clearly the purposes of the study and the manner in which they can contribute to the data collection.

#### 10.7.5. Documentary Review

The study team performed an in-depth documentary review of EMA-related documentation. Next to the legal background documents, the list of documents analysed by the study team can be found in Chapter 8.

#### 10.7.6. Member State Case Studies

A total of 8 Member State Case Studies conducted. The table below presents an overview of the interviews undertaken in each Member State.

**Table 26: Member State Case Studies**

Member State	Interviews undertaken
<b>Czech Republic</b>	<ul style="list-style-type: none"> <li>▶ SUKL</li> <li>▶ Revma Liga Česká republika</li> </ul>
<b>Denmark</b>	<ul style="list-style-type: none"> <li>▶ Danish Medicines Agency</li> <li>▶ Danske Patienter</li> <li>▶ The Danish Generic and Biosimilar Medicines Association</li> </ul>

<b>Estonia</b>	<ul style="list-style-type: none"> <li>▶ Estonian State Agency of Medicines</li> <li>▶ Eesti Patsientide Esindusühing</li> <li>▶ Ravimitootjate Liit</li> </ul>
<b>Germany</b>	<ul style="list-style-type: none"> <li>▶ Federal Institute for Drugs and Medical Devices</li> <li>▶ Paul Ehrlich Institute</li> <li>▶ BAG Selbsthilfe</li> <li>▶ vfa</li> </ul>
<b>Italy</b>	<ul style="list-style-type: none"> <li>▶ AIFA</li> </ul>
<b>Portugal</b>	<ul style="list-style-type: none"> <li>▶ INFARMED</li> <li>▶ APOGEN</li> <li>▶ EVITACANCRO</li> <li>▶ Faculty of Pharmacy of the University of Lisbon</li> <li>▶ EUFEPS</li> <li>▶ APIFARMA</li> </ul>
<b>Spain – replacing France</b>	<ul style="list-style-type: none"> <li>▶ AEMPS</li> <li>▶ Foro Español de Pacientes</li> </ul>
<b>Sweden – replacing Poland</b>	<ul style="list-style-type: none"> <li>▶ Läkemedelsverket</li> <li>▶ LIF – de forskande läkemedelsföretagen</li> </ul>

10.7.7. Product Case Studies

**Table 27: Product Case Studies**

Product
<b>Centralised Procedure – Initial Marketing Authorisation</b>
<ul style="list-style-type: none"> <li>▶ Entresto</li> <li>▶ Lamzede</li> <li>▶ Kanuma</li> <li>▶ Fampyra</li> <li>▶ Tresiba</li> <li>▶ Strimvelis</li> <li>▶ Humanza</li> <li>▶ Benepali</li> <li>▶ Atazanavir</li> </ul>

**Centralised Procedure – Post-Marketing Authorisation**

- ▶ Keytruda
- ▶ Tecfidera
- ▶ Erivedge
- ▶ Elaprase
- ▶ Cayston

**Decentralised Procedure / Mutual Recognition Procedure (to be finalised)**

- ▶ Rapibloc
- ▶ Ibuprofen
- ▶ Sunitinib
- ▶ Flutiform
- ▶ Medikinet Retard
- ▶ Livazo / Alipza
- ▶ Quinolone & Flourquinolone
- ▶ Valporate
- ▶ Hydroxyethyl Starch

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