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Accompanying document to the

Proposal for a

REGULATION OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL

amending, as regards pharmacovigilance of medicinal products for human use, 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

and the

Proposal for a

DIRECTIVE OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL

amending, as regards pharmacovigilance, Directive 2001/83/EC on the Community code relating to medicinal products for human use

Annexes

to Report on the Impact Assessment of strengthening and rationalising EU Pharmacovigilance

SUMMARY OF PUBLIC CONSULTATION RESPONSES

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The first part of the consultation had the objective of collecting the views of stakeholders on the community pharmacovigilance system in general, including comments on the current functioning of the system and how it might be further developed. The first part of the consultation was conducted between 16 March 2006 and 12 May 2006 (although late responses were accepted up to July 2006) with consultation documents placed on the Commission DG Enterprise and Industry Pharmaceuticals website. To facilitate the public consultation the Commission services held two workshops in April 2006 in Brussels. On 20 April 2006 a workshop was held with healthcare professional and patient groups and the meeting was also attended by a representative of a thalidomide victim association. On 21 April 2006 a workshop was held with industry groups. In addition to the workshops the consultation was presented to the scientific and policy committees of the European medicines regulatory network. The results of this first part of the consultation led to the announcement in February 2007 of the Commission Pharmacovigilance Strategy and a detailed analysis of the consultation response can be found at:
http://ec.europa.eu/enterprise/pharmaceuticals/pharmacovigilance_acs/index.htm.

The second part of the consultation was based on draft proposals for changes to EU legislation relevant to the safety of medicines. The second part of the consultation was conducted between 5 December 2007 and 1 February 2008 with consultation documents placed on the Commission DG Enterprise and Industry Pharmaceuticals website with a link to "Your Voice in Europe". The consultation document was also e-mailed to those stakeholders who had submitted a response to the first part of the consultation in 2006. In addition, to facilitate the provision of consultation responses by medicines regulators, the consultation was presented in detail to the scientific and policy committees of the European medicines regulatory network. The public consultation document and a detailed analysis of the consultation response can be found at: http://ec.europa.eu/enterprise/pharmaceuticals/pharmacovigilance_acs/index.htm.

Overview of comments on the Commission's public consultation entitled "Assessment of the Community System of Pharmacovigilance" (16 March 2006 to 12 May 2006)

The European Commission conducted a public consultation entitled 'Assessment of the Community System of Pharmacovigilance'. Interested parties were invited to submit their comments between 16 March 2006 and 12 May 2006. To facilitate the public consultation the Commission held two workshops in April 2006 at its offices in Brussels. On 20 April 2006 a workshop was held with healthcare professional and patient groups and the meeting was also attended by a representative of a thalidomide victim association. On 21 April 2006 a workshop was held with industry groups.

CONTRIBUTERS

The Commission consultation received 48 contributions. In summary:

- Ø 7 responses from patient, consumer and victim groups.
- Ø 10 from healthcare professional groups of which 4 represented doctors, 3 pharmacists and one nurses.
- Ø 16 from industry including all the relevant European Industry Associations.
- Ø 10 from regulators including the European Medicines Agency Committees and individual medicines agencies.
- Ø 5 others, including the WHO Uppsala Monitoring Centre and the International Society for Pharmacoepidemiology.

OVERVIEW OF COMMENTS RECEIVED

In addition to the individual responses being posted on the web[1], this section provides high level summary of the key consultation messages .

Legal framework and its implementation

The vast majority of responses call for a **change to the legal framework for pharmacovigilance** in the EU, either explicitly or by requesting changes to the system which could only be realised through a change to EU law. The pharmaceutical industry makes a strong **call for rationalisation of the legal framework** calling the **current legal framework contradictory, confusing, unclear and complex**. The fact that the different Member States have slightly different rules, including requirements going beyond those in EU legislation is highlighted, including the cost implications of these differences and the fact that this **interferes with the operation of the European single market** and the free movement of goods. The lack of harmonisation is suggested to be **detrimental to public health** as it diverts resources away from safety monitoring towards meeting disparate administrative requirements. While the European industry associations representing the innovative industry and biotechnology industry together with the German pharmaceutical industry association and a major European innovative company explicitly call for **a single Council regulation on pharmacovigilance to replace all existing EU laws**, the European association representing the non-prescription industry calls for a period of stability with harmonisation at the level of EU guidance (despite the fact that this might contradict EU and National law). Additional comments on the legal framework include a **need for better regulation** and a call from the European regulators (the Committee on Human Medicinal Products and its

[1] http://ec.europa.eu/enterprise/pharmaceuticals/pharmacovigilance_acs/icr.htm

Pharmacovigilance Working Party) for a change of legislation on periodic safety update reports (PSURs), renewals, **clear legal roles, responsibilities and accountability** and notifications of major drug safety announcements. Both the industry and regulators call for the **pharmacovigilance system to be strengthened**.

The consultation was conducted in parallel with a consultation on the main EU guideline on pharmacovigilance: Volume 9a of Eudralex. Perhaps because of this, a number of comments on implementation focussed on Volume 9a including the fact that it only exists in English, that some provisions were unclear and others of questionable legal basis and enforceability. Further comments suggested that a comparison of the divergent requirements in the Member States should be conducted and made public. There is a call for the pharmacovigilance **requirements placed on industry to be determined by the level of knowledge about the drug** i.e. not having the same requirements for all products.

Resources

There is a strong call, particularly from the regulators and academia for **increased resources in pharmacovigilance**. This includes funding and experienced staff for regulatory pharmacovigilance, as well as funding of research into the **methodologies of pharmacovigilance, epidemiological studies, drug safety communication and audit** (both quality management and outcome monitoring). There was a particularly **strong call for more public funding** with a small number of responders calling for funding to be entirely public. A call for funding from the **European Commission Framework Programmes** was clear particularly from the regulators. A strong message from industry, regulators and academia is that current **duplicative reporting requirements lead to wasted resources and inefficiency.**

Organisation of the pharmacovigilance system

In terms of organisation within the EU, divers but potentially complimentary messages come from the consultation. While there is a clear call for **harmonisation** of requirements in the Member States, there are calls for more regional centres, centres of excellence, a focus on the overall EU system rather than disparate Member State systems with **only one procedure in Europe** and a clear message, particularly from the regulators, that the **Member States have a crucial role to play** in the conduct of pharmacovigilance.

A small number of responders call for **greater collaboration with international partners** including the World Health Organisation and non-EU drug regulators. Three responders suggest that medicines **regulation and industry competitiveness should be split** at the level of the European Commission. Additionally responders suggest that within the regulatory agencies the **authorisation of medicines should be split from pharmacovigilance** to ensure that decision-making on safety issues is independent.

Transparency and stakeholders

Sixteen responders explicitly commented on transparency, with all **calling for increased transparency**. These calls for increased transparency related to all steps in the pharmacovigilance process and came from all stakeholder groups (although most strongly from patients, consumers and regulators).

European patient groups in particular but also some health professional groups and regulators call for **increased collaboration between stakeholders**, particularly **engagement with patient groups**. The key role of pharmacists and the need to work with academia were also highlighted.

Roles, responsibilities, inspections and compliance

EU legislation requires a marketing authorisation holder (a company holding a licence for a medicine) to have a "**qualified person" for pharmacovigilance**. While the regulators call for a change whereby the qualified person would be identified with a corporate entity, some sections of the industry call for flexibility. A specific suggestion is that **the supervisory authorities for pharmacovigilance**, currently defined in EU legislation as the Member State where the manufacturing authorisation is issued, should in fact **be the Member State where the qualified person resides**.

Patient groups, regulators and some industry associations call for a **greater focus on industry compliance including inspections** (and establish clear standards for inspections). Regulators and academia call for **greater regulatory power over industry in the post-authorisation period** (e.g. the **power to force companies to conduct studies** and stronger powers in case of non-compliance).

Current legislation requires industry to submit a detailed description of its pharmacovigilance system with each marketing authorisation application. The law then requires any change to be via a variation to the marketing authorisation (which requires an application and regulatory approval). European industry and regulators suggest that scrutiny of industry systems should remain but bureaucratic burden should be reduced by **establishing a new legal concept the "pharmacovigilance system master file**" which would be maintained by companies, submitted on request and **subject to inspections**.

An interesting suggestion from academia is to create a requirement for all clinical trial results to be scrutinised by the regulators in the post-authorisation period.

Adverse Drug Reaction (ADR) reporting

Eleven consultation responses **explicitly call for the introduction of consumer reporting** of ADRs (which is currently excluded by legislation). This call comes from European patient and consumer groups as well as some regulators, industry, academia and the World Health Organisation.

Thirteen consultation responses including all the main European industry associations, as well as, some regulators, academia and patients call for a rationalisation and simplification of the ADR reporting requirements for industry and regulators (that are currently dictated by EU law). They point out that there is enormous duplication of effort with a single report circulating between numerous senders and receivers. The waste of resource is highlighted, as well as the fact that the resource could be reallocated to better public health protection. The role of the European pharmacovigilance database "Eudravigilance" is highlighted as being key to the rationalisation and simplification of the system. Eleven responses explicitly call for all ADR reports to be submitted to one single point, that being Eudravigilance. No responders argue for maintaining the current multiple reporting.

The **costs of electronic reporting** particularly for small and medium sized enterprises are highlighted by a number of industry responses and one of the suggested solutions is to have one set of standards applicable across the EU. The **duplication of effort and administrative burden of reporting ADRs published in the literature is highlighted**. The fact that all marketing authorisation holders have the same requirement for reporting cases published in the literature, leading to hundreds of duplicate reports being submitted, leads the industry associations to call for rationalisation of the requirements.

Numerous suggestions are made on how **ADR reporting** from healthcare professionals and patients could be **stimulated** including ways to facilitate reporting such as internet and

telephone reporting and having consumer reporting forms or reminders on patient information leaflets.

Other data sources

European patient groups, academia, European regulators and the World Health Organisation are all calling for greater use of more robust data sources rather than relaying mainly on spontaneously reported suspected ADR reports ("**move up the evidence hierarchy**"). Specifically there is a **strong call** for a dramatic **increase in the number of post-authorisation safety studies**, both those conducted by industry and independent academic studies. Regulators and academia call for such studies to be mandatory while patient and consumer groups call for **stronger regulation of non-interventional studies**.

Industry, regulators and academia call for **investment into databases and other data sources** that can be used **for pharmacoepidemiological studies**, together with increased training in pharmacoepidemiology and networking of academics in Europe (to increase capacity and exchange best practice).

The bureaucratic burden and **waste of resources for both industry and regulators** of the current requirements for **Periodic Safety Update Reporting** are highlighted by industry, regulators and academia. Responders call for rationalisation of the reporting with a **clear legal basis for work sharing** by both industry and the regulatory authorities.

Data management and safety issue detection

Industry and regulators call for full utilisation of Eudravigilance, the European pharmacovigilance database, including financial and human resource investment.

Patients, academics, regulators, industry associations and the World Health Organisation call for routine use of statistical methodologies in signal detection, including international collaboration.

Assessment and decision-making

Industry and academia call for the power to **compel industry to conduct post-authorisation safety studies**, in the event that a safety issue is detected or suspected.

There is cross-sector support for **patient involvement in decision-making** with additional calls for involvement of victims of adverse reactions, healthcare professionals and industry. There is a clear call for routine use of external experts and of peer-review.

With respect to the **European referral system** there is a clear message from across the stakeholder groups that there should be **rationalisation of the system** with fast, streamlined, legally binding decisions and focussed rational input from the affected industry. The industry particularly emphasises the need for **more European rather than divergent Member State decisions** on drug safety issues.

Regulatory action, risk minimisation and risk management

Risk management plans are highlighted as **key** tools in pharmacovigilance although the regulators stress the **need for a legal requirement that companies complete the data collection** specified in plans.

The European Medicines Agency calls for a new simple system whereby generic companies would have to follow the innovator when changes to product information relevant to the safety of products need to be implemented.

Patient groups call for **new products to be labelled as such** for their first two-years on the market so that patients can make informed choices. Such a system could also be used to stimulate reporting of suspected ADR with new products.

Education and decision-support for prescribers, dispensers and users of medicines is a strong theme of many consultation responses. Many call for **integration of drug safety information into prescribing and dispensing systems,** while others call for education about reporting suspected adverse reactions. The need for **funding** is highlighted.

Communication

Patients, industry and regulators call for greater European harmonisation and coordination of drug safety communications. The regulators call for a strong legal requirement for the industry to have to inform regulators prior to making major safety announcements, such as product withdrawals. Industry calls for clear contact points with the regulatory authorities ideally with one contact per authority.

Various responses stress the importance of getting quality information on important drug safety issues to the various stakeholders in a timely manner. Amongst these are specific practical suggestions which could improve the system. **A stakeholder partnership / forum on drug safety communication** is proposed.

Outcome of regulatory action and quality management

A strong message from across the stakeholder groups is the **need to routinely monitor the outcome of regulatory action** to ensure that public health has been adequately protected / promoted. The need for outcome monitoring to be a **legal requirement,** as well as, the need for it to be **resourced** is highlighted.

All stakeholder groups call for **quality management in pharmacovigilance** with clear standards ("**Good Pharmacovigilance Practice**") and **routine audit**. The link to improved public health is highlighted.

Pharmacovigilance for herbal medicinal products

The European Medicines Agency's committee for herbal medicinal products, as well as one academic working in herbal safety have provided important consultation responses which highlight the need for robust pharmacovigilance for herbal medicines and the peculiarities of herbal medicines including how they are sold and used. The **need for guidance on herbal pharmacovigilance** is one important recommendation made.

CONCLUSIONS

The Commission consultation "Assessment of the Community System of Pharmacovigilance" received 48 written responses representing the views of the spectrum of stakeholders. Compelling arguments are provided that the current complex system leads to wasted resources, a focus on bureaucracy rather than health protection and is a barrier to the marketing of effective products to European patients. **There was a strong and clear demand from all stakeholder groups for the Community pharmacovigilance system to be strengthened and rationalised.**

Analysis of the results of the Public consultation on legislative proposals

INTRODUCTION

The services of the European Commission have publicly consulted stakeholders on its Strategy to Better Protect Public Health by Strengthening and Rationalising EU Pharmacovigilance. The second part of the consultation, based on draft proposals for changes to EU legislation relevant to the safety of medicines, was conducted between 5 December 2007 and 1 February 2008. To facilitate the provision of consultation responses by medicines regulators, the consultation was presented in detail to the scientific and policy committees of the European medicines regulatory network.

CONTRIBUTERS

The Commission consultation received 82 contributions. In summary:

- Ø 5 responses from patient and consumer groups
- Ø 16 from healthcare professional groups and academics
- Ø 26 from regulators including the European Medicines Agency Committees, individual European medicines agencies and regulatory authorities outside the EEA.
- Ø 29 from industry including all the relevant European Industry Associations
- Ø 6 others, including the European Monitoring Centre for Drugs and Drug Addiction, the International Network of Safe Medication Practice Centres, the International Society of Drug Bulletins, and European and International health insurance associations.

OVERVIEW OF COMMENTS RECEIVED

In this section a high level summary of the key consultation messages is provided. In addition, the individual responses will be placed on the Commission website.

1. General Feedback

There was very strong support for the objectives pursued and for the draft proposals overall with only two of eighty-two responses not welcoming the proposals. There was strong support for improving the robustness of EU pharmacovigilance with clear legal provisions and better use of resources i.e. resources used to monitor the safety of medicines and take action to reduce risks to users rather than used to meet duplicative administrative requirements.

2. Legislative Strategy

Relatively few stakeholders commented on the legislative strategy as such (i.e. a directive of the European Parliament and the Council amending Directive 2001/83/EC and, a regulation of the European Parliament and the Council amending Regulation (EC) No 726/2004). Those

that did were mostly supportive although some industry responses commented that use of a directive could lead to disharmony through Member State transposition / implementation.

3. Rationalise EU decision-making

There was unanimous support for the need to rationalise EU decision-making on safety issues.

This support included strong endorsement for the establishment of an automatic pharmacovigilance referral procedure with non-discretional referral triggers placed on the Member States. Questions were raised and suggestions made regarding the scope of products covered by the procedures (notably whether centrally authorised products were included) while the scope of the triggers was generally supported (with reservations from a minority of industry responses about inspection findings being a trigger).

The proposed operation of the referral procedures was generally supported, however, numerous comments were made on the detail. The more consensual of the latter were that companies should be notified of referrals affecting their products, be consulted more explicitly and have an appeal procedure, that divergences in the views of the committees would need careful handling, and that the existing Coordination Group for Mutual Recognition and Decentralised procedures – Human (CMD-H) could have a role in implementation of decisions. There was unanimous support for the outcome of the referrals being legally binding. The proposal to hold public hearings for all but the most urgent referrals received a mixed response. While consumers and doctors strongly welcomed the proposal for hearings, regulators and industry expressed some concern that public hearings would be resource intensive and should not be systematic (there was, however, a reasonable level of support for ad-hoc public hearings).

The proposal to create a new Pharmacovigilance Committee with a clear legal identity and defined remit was almost unanimously supported. However, many stakeholders called for greater clarity on the precise remit of the new committee, its role on centrally authorised products (which was not specified in the consultation document) and its interface with the existing committees notably the Committee on Human Medicinal Products (CHMP) and CMD-H. There was a very wide spectrum of suggestions on remit, from the new Pharmacovigilance Committee having complete autonomy from the existing EMEA Committees for post-authorisation issues and total authority in decision-making, to stakeholders wishing the CHMP to have complete authority over benefit risk assessment with emphasis put on the importance of the knowledge and expertise brought by the authorisation rapporteur team and from the integration of pre and post-authorisation assessment. The important role of the CMD-H was stressed particularly with respect to nationally authorised products and a role for CMD-H in decision-making and implementation of decisions was suggested. Regarding the composition of the new Pharmacovigilance Committee there was support for patient and healthcare professional representation, as well as, support for maximising the pharmacovigilance expertise available. Linked to the latter point, some stakeholders called for pharmacovigilance experts to be selected rather than being appointed by Member States.

4. Rationalise roles and responsibilities / establish clear standards

There was unanimous support for clarifying and rationalising the roles and responsibilities of those stakeholders having requirements provided for in the pharmacovigilance legislation. Some stakeholders suggested providing explicit tasks for healthcare professionals and patients in the legislation (despite the EU Treaty base for the legislation and subsidiarity principles being against this) and two responders suggested that the role of industry in pharmacovigilance was too great.

The proposal for strengthening the obligation on industry to inform about changes to the benefit risk balance of its products including when this results from clinical trial results was generally welcomed with regulators suggesting the provision on clinical trial reporting be even more explicit and industry suggesting a need for greater clarity and the requirements to be delineated. There was similary support for the new obligation on industry to keep its product information up to date with regulators suggesting that labelling recommendations on the EMEA website should be more binding and industry requesting greater clarity of the scope of the requirement.

There was strong support for the principles of outcome and process audit although greater clarity was requested on the processes for these functions. Similarly, inclusion of requirements for monitoring safety data and signal detection were welcomed although more precise provisions and delineations of responsibility were suggested (notably with a key role for the new Pharmacovigilance Committee suggested).

Among the small number of stakeholders who commented, there was support for the proposal that Member States may delegate certain pharmacovigilance tasks to each other although there was a request for details on the scope of tasks.

There was unanimous support for the introduction of Good Vigilance Practices (GVP) with suggestions for broad stakeholder involvement in its (early) development and respect for existing international harmonisation with diverse comments on the proposed scope and the interface with existing EU guidance (i.e. Volume 9A of Eudralex).

The proposal for an overarching provision obliging the Member States to enforce penalties for non-compliance with pharmacovigilance provisions were broadly welcomed with industry requesting a clear definition of the Member State measures, procedures and an appeal mechanism.

5. Company pharmacovigilance system and inspection provisions

There was strong support for rationalising the way the authorities oversee the company's pharmacovigilance system. The proposals will allow companies to make changes to their systems in a timely manner while also maintaining oversight by the authorities. Five of eighty-two stakeholders interpreted the proposal to submit a summary of the pharmacovigilance system at authorisation and maintain a detailed dossier on site in the form of a 'Pharmacovigilance System Master File - PSMF' as reducing regulatory scrutiny. However, this may have been because the consultation paper insufficiently emphasised that the current very bureaucratic system obstructs companies from having a modern, flexible system and that the new proposals include wide ranging powers for the authorities to request submission of the PSMF and to send inspectors to the companies who would have to provide access to their premises and the PSMF. Industry voiced strong concerns about internal audit reports being included in the PSMF.

Amongst the relatively few comments on the proposals to increase EU coordination of pharmacovigilance inspections was the suggestion for the EMEA to maintain a database of reports, the suggestion for a risk based system to be introduced, and the suggestion for minimum EU inspection standards to be developed. The industry requested clarity regarding the process for audit reports and company comments on them, and on the interface with GMP inspections. Guidance was requested on the concept of 'serious deficiencies'.

Regarding the proposal to create a specific supervisory authority for centrally authorised products for the purposes of pharmacovigilance inspections, the industry suggested that the site of the main pharmacovigilance function rather than the country of residence of the Qualifies Person should dictate the authority and there were various questions raised on the scope of responsibilities of the authority.

6. Rationalise and strengthen risk management planning

There was very strong support for rationalisation and strengthening of the role of risk management planning in pharmacovigilance thereby making safety monitoring and risk minimisation driven by the knowledge of the safety of a product, more proactive and based on more robust data. There was a request for the terms risk management system and risk management plan to be merged and for the follow up and maintenance of risk management plans to be clarified. There was a call for clarity on which products would need a risk management plan submitted at authorisation application but unanimous agreement that the key measures in the plan be made legally binding by their inclusion as conditions of the marketing authorisation (although it was suggested that key elements / a summary of the risk management plan be annexed to the marketing authorisation rather than the entire plan). Industry requested one EU risk management plan without the need for Member State negotiations and amendments.

There was broad support for the introduction of 'intensive monitoring' and an 'intensive monitoring list' for new products with studies, additional safety monitoring or restriction on use as risk management conditions in the marketing authorisation. There were requests for clarification on whether the provisions were aimed at all new substances, could be applied whatever the authorisation route and on the inclusion criteria, maintenance process and removal mechanism of the intensive monitoring list. Additional comments included the need to explain the purpose of the list to stakeholders and the need to include already authorised products on the list. A role for the Pharmacovigilance Committee in overseeing the list was suggested.

There was strong objection to the proposal to replace the current 'exceptional circumstances marketing authorisation' with the 'intensively monitored' products. The intention was to increase the robustness of post-authorisation follow up of the majority of new innovative products by applying to them the annual reassessment process currently used for 'exceptional circumstances marketing authorisation' products. The objections fell in to two groups: 1. those that considered that 'exceptional circumstances marketing authorisations' were useful for non pharmacovigilance related issues, and, 2. those that understood the proposal to be a lowering of the standard for placing a product on the market. While the first objection may be justified, the second is a misinterpretation of the effect of the change.

The consultation paper also proposed to amend the criteria for taking regulatory action post authorisation (amendments to Articles 116 and 117 of Directive 2001/83/EC) simplifying the criteria basing them on the benefit risk balance (deleting the sub clause of efficacy) and deleting the concept of normal conditions of use as this is not defined and could be interpreted as restricting regulatory action in the case of a major public health issue related to off-label use (e.g. in children). The proposals then brought the authorisation criteria in line to have a rational symmetry of criteria for putting a product on and taking it off the market. While some industry responses question the deletion of normal conditions of use, major objections were received regarding deletion of the efficacy sub-clause. Some stakeholders understood this to mean that products without efficacy could be put on the market i.e. a lowering of the

requirements for authorising a medicine. It appears that the rational for the proposed changes and particularly the concept of efficacy being a sub clause of benefit risk (a positive benefit risk being impossible with no efficacy) was not well explained in the consultation paper.

7. Legal basis for requesting PASS

There was unanimous support for a clear legal basis for the authorities to request post authorisation safety studies (PASS). There was also support for the proposed procedure and for the inclusion of the final requirement as a condition of the marketing authorisation thereby making it legally binding.

The consultation paper proposed an inclusive definition of post-authorisation safety study which thereby defined the scope of studies which could be requested in the event of serious safety concerns. There were diverse comments on the definition, many positive and supportive, however, some industry responses suggested a narrower definition and this may be explained by a misunderstanding of the purpose of the definition, considering it to define the scope of regulatory oversight of studies (rather than defining the scope for requesting them).

8. Post-authorisation safety studies (PASS) - principles and oversight

There was strong support for guiding principles and oversight of a subset of PASS, that subset being non-interventional PASS, initiated, managed, or financed by the marketing authorisation holder and that involve collection of data from healthcare professionals or patients. Some industry responses questioned the precise limits of the scope of the oversight including whether non-EU studies are included (they explicitly are not), while some responses from both industry and regulators called for the interface with risk management plans to be clarified. The guiding principles were supported while having a scientific objective was also suggested as such a principle. The key comments on the procedure were for protocol suggestions from the regulators to be binding and support for making public recommendations for product labelling based on the study results. Some stakeholders suggested that such recommendations should be legally binding.

9. Rationalise single case adverse drug reaction reporting

The proposals to strengthen and rationalise expedited single case adverse drug reaction reporting received very strong support including strong support for simplification of the rules based on electronic reporting with full utilisation of modern information technology. The important role of Member States, and for some countries, of regional centres in stimulating reporting and improving the quality of reports was emphasised. Numerous stakeholders from across the different groups suggested that the causality criteria that had been proposed needed amending or that the concept of suspected adverse reaction should be maintained.

There was strong support for the use of Eudravigilance as a common tool to support pharmacovigilance and stakeholders stressed the importance of national regulators and companies (i.e. those with legal responsibilities for safety monitoring) having full access to the data on Eudravigilance (for transparency see Section 11). A small number of stakeholders expressed concern about the technical capabilities of the Eudravigilance 2007 version and emphasised that further development would be necessary to support the proposed new pharmacovigilance rules.

There was unanimous support for marketing authorisation holders electronically reporting all serious non-EU adverse reaction cases to Eudravigilance only. In contrast the proposal that all EU domestic reports be electronically reported to Eudravigilance and thereby be made available to the Member States received mixed feedback: while five regulator responses suggested that reports should be send to Eudravigilance and the country of origin of the report, the industry supported reporting only to Eudravigilance but suggested that non-serious reports should be electronically reported periodically rather than on an expedited basis.

There was strong support for the principle of providing a clear legal basis for patient reporting although numerous suggestions were received on how this should be best achieved. The important role of healthcare professionals in interpreting symptoms and signs was stressed as was the relationship between patient and professional. Overall there was support for making a variety of methods available to patients to report there suspected adverse reactions. There was support for information on adverse reaction reporting to be included in patient information leaflets of intensively monitored products while the inclusion of forms in packaging was not encouraged. It was suggested to introduce a symbol onto the packaging of intensively monitored products rather than having a warning on the packaging. The draft proposals suggested that paper reports be sent by patients to the marketing authorisation holders in order to distribute the work of the data entry necessary for electronic reporting and data management. However, there was a strong call, including from the regulators, for patient reports to be send directly to the national competent authority for medicines.

The proposal that the EMEA make available within five-years a web-based structured reporting facility to Eudravigilance was strongly welcomed by patient and healthcare professional groups. In contrast some regulators saw this as bypassing the national medicines authority and being detrimental to data quality.

With the exception of the European Medicines Agency (EMEA) itself, there was unanimous support for the EMEA having a core but delineated role in literature monitoring and reporting to Eudravigilance of adverse reaction case reports. The high work load involved in literature monitoring was stressed as was the fact that because of reporting requirements to non-EU regulators, EMEA processes would have to be transparent, meet strict criteria and the data in Eudravigilance would have to available to the marketing authorisation holders for them to then be spared duplicating the work. Furthermore, the industry suggested that the resource saving for new innovative drugs would not be major as marketing authorisation holders would wish to carefully monitor the literature independently of any legal reporting requirements. Linked to this point was a suggestion that the EMEA role be limited to old established products (i.e. be based on active substances where there was no patent or regulatory data protection). It was emphasised that there would need to be clarity as to whether the marketing authorisation holders still had to monitor local market literature and non-EU regulators and the industry pointed out that this would be an opportunity for international collaboration including on monitoring standards.

There was strong support for clarifying the place of medication error reporting within regulatory pharmacovigilance. Comments called for greater clarity of the provisions particularly the respective roles and responsibilities of the different parties, however, amongst those expressing a view there was support for placing an obligation on Member States to ensure exchange of data between the competent authority for medicines and any national authority responsible for patient safety. The need for data to be submitted to Eudravigilance, the need for such reports to be earmarked in the database (for data analysis) and the need to address anonymous reporting were highlighted. It was suggested that "near misses" and not

just medication errors resulting in an adverse reaction should be reported within the regulatory pharmacovigilance system.

Amendments and deletions to certain definitions related to adverse reactions were suggested in the consultation paper. The simplification of the definition of adverse reaction was proposed to support medication error reporting and certain other definitions were proposed for deletion as they were considered redundant as far as legal provisions were concerned. These proposals stimulated numerous comments including the need to respect internationally agreed definitions, as well as, an array of suggestions for new definitions. Although the proposed amendment of the definition of "adverse reaction" received both negative as positive comments, no clear rationale was provided against the proposed change.

To improve the pharmacovigilance of biological products including biosimilars the consultation paper proposed that Member States ensure that biological medicinal products that are the subject of adverse reaction reports be identifiable. This proposal resulted in numerous comments mainly from the industry. While some responses suggested that delegating this responsibility to the Member States could result in disharmony (and proposals for the Pharmacovigilance Committee to issue guidance were put forward) the innovative industry sector suggested that the EU legislation be used to force distinct names (distinct INNs) for biosimilar medicinal products and to outlaw biosimilar substitution at the level of the pharmacy.

10. Rationalise periodic safety update reports (PSURs)

There was strong support for rationalisation of periodic safety update reports (PSURs). There was support for linking PSURs to risk management planning but a call for this link to be more explicit. The reorientation of PSURs to be risk benefit evaluations including assessment of all relevant data rather than including data line-listings was supported although concerns were expressed about the impact on internationally agreed formats.

There was full support for PSURs to be submitted electronically with strong industry support for exclusive submission to the Pharmacovigilance Committee and thereby distribution to the rapporteurs and Member States, while three Member State authorities suggested that the authorising authority should also be send a report directly by the Marketing Authorisation Holder. The need to define, test and implement a standard for electronic PSURs was emphasised.

It appears that the proposals to rationalise reporting for old established products were not sufficiently explained in the consultation paper. The intention in the consultation paper is that routine, uncoordinated PSURs for old established products should not be a default requirement of the legislation but rather that the Pharmacovigilance Committee would build on the existing work-sharing project being conducted by the Heads of Agencies and Pharmacovigilance Working Party. Specifically, based on a judgement of the Pharmacovigilance Committee of the risk posed, including the need for product information to be updated, PSURs covering a specified period of time would be required to be submitted by a deadline for all products containing a particular active substance. Because the proposals were not sufficiently explained the comments received were diverse with many incorrectly interpreting that no PSURs would ever be submitted for older products. The comments received are, however, supportive of some PSUR reporting for older products based on risk and for this to be rationalised.

In terms of the procedure for PSUR assessment, there was overall strong support for a key role for the Pharmacovigilance Committee including making public its recommendations for product labelling. Medicines regulators called for the recommendations to be more binding over the companies.

11. Strengthen transparency and communication

There was unanimous support for the need to strengthen transparency and communication in pharmacovigilance. Many stakeholders emphasised that risk information should not be presented in isolation but be balanced with information on the benefits of medicines and the importance of respecting both commercial and personal data confidentiality was stressed. The need for stakeholder engagement and consultation was also emphasised by different stakeholder groups.

The proposal for both EU and National medicines safety web-portals was strongly supported although clarity regarding the interface with existing websites such as the Commission Public Health Portal and EMEA EudraPharm was requested. The spectrum of information to be made public was broadly supported although the diverse and divergent comments can be summarised as, on the one hand requesting that only summaries of final documents and conclusions to be added to the website and, on the other hand that a much greater level of transparency be implemented including all correspondence and interim assessments.

The proposals on increased transparency of adverse reaction data on Eudravigilance were welcome except by some industry responses. The need to make public aggregated adverse reaction data which is clearly presented and explained for stakeholders in an EU-agreed format was emphasised. Proposals for details of individual reports to be released on request were welcomed by many stakeholders but concerns were expressed about personal confidentiality not being respected and regarding the workload involved.

There was strong support for enhanced EU coordination of important safety messages including the timing of their distribution. The industry requested that the proposals go further in committing the Member States to single EU safety communications while the Member States stressed the importance of local factors and cultural elements.

The proposals on the provision of medicinal product information to support the development of EudraPharm and the EU pharmacovigilance medicinal products dictionary raised comments regarding the scope of the work and the interface with ongoing projects. Notably, clarity was requested as to whether the intent was to feed EudraPharm or the EU pharmacovigilance medicinal products dictionary or both and the need for respect of the ongoing ICH and ISO projects was emphasised. It was suggested to limit the scope to authorised medicinal products and to prolong the deadlines on industry.

12. Strengthen product information

Stakeholders were strongly supportive of the need to improve EU product information including the penetration of key information including safety information. Stakeholders emphasised that safety information should be presented in the context of benefit and that a synthesis of key information was need rather than a presentation of only key safety information. There were suggestions for a key information or summary section to be added to the beginning of product information and a strong call for measures based on key information to be supported by detailed guidelines developed based on wide consultation and careful

testing. The industry requested a long implementation phase to minimise the cost implication of the proposed changes.

13. Other major comments not falling into sections 1 to 12

The comments received are diverse and readers may wish to read the individual comments for themselves (see Section 13 of Annex 1 of the detailed analysis at: http://ec.europa.eu/enterprise/pharmaceuticals/pharmacovigilance_acs/index.htm). However, one issue warrants highlighting.

A small number of responses understood the consultation paper as being driven by a desire to increase the competitiveness of the pharmaceutical industry by allowing early market entry rather than a desire to improve public health protection. This is not incorrect. This misinterpretation may have been due to the emphasis the introduction to the consultation paper placed on the effects of robust pharmacovigilance on stimulating innovation. It is undeniably true that regulators are more likely to grant a marketing authorisation if they are sure that robust safety monitoring and follow up of the product will be in place i.e. of robust pharmacovigilance. The link between robust pharmacovigilance and the authorisation of new medicines is clear and this will have a positive effect in terms of stimulating innovation which in turn has positive health (fulfilling the unmet medical needs of patients with serious diseases) and industrial impacts. It must be emphasised the proposal is fundamentally a public health one which aims to protect EU public health by reducing the mortality and morbidity associated with adverse drug reactions. Any positive industrial impact is a side effect of the proposal.

COMMISSION OF THE EUROPEAN COMMUNITIES

Brussels, 17 September 2008

COMMISSION STAFF WORKING DOCUMENT

Annex 2 of the Report on the impact assessment of strengthening and rationalising EU Pharmacovigilance

EVOLUTION OF THE SPECIFIC POLICY OPTIONS

1. Public health burden of Adverse Drug Reactions

Introduction

Adverse drug reactions (ADRs) are a common cause of morbidity and mortality with a considerable adverse impact, not only on the health of the population, but also on health care costs and represent a burden that diminishes the true value of modern drugs. There is increasing acceptance that ADRs are partially avoidable and some of the potential benefits that could be reached by efficient preventive measures, are:

- Ø reduced mortality (deaths),
- Ø reduced morbidity, sick leave days and impaired days,
- Ø reduced potential disabilities,
- Ø reduced number of hospital stays and out- patient care.

A cost analysis of ADRs also raises an issue of the perspective of the analysis, which is important as certain costs or benefits may not be relevant for all parties. The social perspective is often preferred in pharmacoeconomic evaluations and is supposed to include all relevant costs. An analysis of the costs of ADRs from a social perspective is, however, difficult to perform as most ADRs are mild and do not lead to contact with medical care.

The negative social and economic effects of ADRs to any society could be further classified as:

- Ø **Direct costs:** refer to costs falling on the health sector in relation to prevention, diagnosis and treatment of disease, e.g. ambulances, inpatient, outpatient, rehabilitation, community health and medical services, and pharmaceuticals.
- Ø **Indirect costs:** typically measure the lost productivity potential of patients who are too ill to work or who die prematurely (i.e. the 'human capital approach'). The measurement of indirect costs is a matter of much debate. Some Cost of Illness studies consider the loss of future earnings, discounted to take account of the fact that the income will arise in the future, while others are based on the 'willingness to-pay method'.
- Ø **Intangible costs**: capture the psychological dimensions of the illness to the individual (and their family), i.e. the pain, bereavement, anxiety and suffering. This is the cost category that is typically hardest to measure. The output of Cost of Illness studies, expressed in monetary terms, is an estimate of the total burden of a particular disease from either a societal or (if a narrower set of costs is included) sector-specific perspective.

There are a number of studies in the literature that focus on direct health care costs resulting from ADRs and on the estimation of the share of all ADRs that are preventable. The estimation of indirect costs is complicated because necessary information to assess the loss of productivity, e.g. employment status, is often difficult to obtain. Moreover the question, which share of the loss of productivity can be attributed to the ADR and which to the underlying disease, is a methodological challenge. Intangible costs related to factors like stress, fear, pain or, in summary, the reduction of health- related quality of life are even more difficult to quantify. Therefore it is not surprising that almost no original research on indirect and intangible costs of ADR could be found and therefore this analysis will concentrate on the direct costs, which represent a substantial part of economic burden resulting from ADR.

Classification of impacts

Adverse effects have an impact both on health and on resource utilisation. Measuring the impact on survival allows quantification of the burden of adverse effects. The benefits of preventing adverse effects, or reducing their frequency and severity, are the reduction of burden. The literature review identified a number of economic analyses of the adverse effects

cost of drugs. They have been carried out with different methodologies and they are therefore not always comparable. These studies, however, demonstrate that a quantitative approach to measuring the impact of adverse effects is feasible.

Measured impacts fall into three categories:

a) Burden of adverse drug reactions that occur during hospitalisation and result in prolonged hospital stays and higher costs, including those arising from surgical needs;

b) Burden of adverse reactions that occur in the ambulatory setting and result in hospital admissions and emergency department visits;

c) Burden of induced ambulatory care, when no hospital admission is required.

Most references provide evidence for ADRs being a common cause of hospitalisation, but hospital admissions are only a part of the total consequences as most ADRs never come to clinical attention. There have been attempts to estimate the total cost of drug related morbidity and mortality and these results provide some idea of the magnitude of the problem, even if estimates are based on assumptions.

The incidence of ADRs

There are several sources that can give information on ADRs and their occurrence. One such source is the clinical trial, which is conducted before the release of the drug on the marked and is primarily designed to show treatment effects and common adverse reactions. A limitation of clinical trials is that the size of the study population and the restricted length of follow-up make it difficult to discover uncommon or delayed effects. Other limitations are that clinical trials often have a selected population and that drug utilisation is highly controlled. Other sources of information are case reports and epidemiological studies, which are conducted after the release of the drug on the market. These sources have a higher chance of finding uncommon effects in a real-world situation, but they are less controlled which makes it more difficult to establish causal relations between drug use and ADRs. The incidence of all ADRs is difficult to estimate and has not been widely studied. The incidence in hospitalised patients and the number of ADRs leading to hospital admissions has, however, been investigated in several previous studies. Table 1 shows an overview of findings in some of these studies.

From Table 1 it can be seen that approximately 5% of all hospital admissions are caused by an ADR and that about 5% of hospitalised patients suffer an ADR. Studies have also shown that adverse events during hospitalisation lead to delayed time to discharge. Bates et al. investigated 190 ADRs from 4108 hospital admissions at medical and surgical departments. On average, each event caused 2.2 days longer hospitalisation time compared with matched controls. Two other similar studies found ADRs to cause 1.91 and 3.5 extra days of hospitalisation.

Lazarou *et al.* have further highlighted the public health importance of ADRs by estimating that ADRs caused over 100,000 deaths in the United States in 1994.[2] This would correspondent to **197,000 deaths** (142,000 if the lower confidence limit was used) when extrapolated to the EU-27 population in 2006. While some methodological criticisms are justified, there is a consistent pattern of ADRs that are high and of real significance to individuals and institutions.

[2] Lazarou J., Bruce H. et al.: Incidence of Adverse Drug Reactions in Hospitalized Patients. JAMA April 15 Vol 279 Nº15, 1998.

Table 1 Incidence and prevalence of adverse drug reaction reported in the literature3

Outcome	Incidence/prevalence	Reference
ADR-related hospital admissions		
Drug-related hospital admissions	4.2%	Einarson [1]
Drug-related admissions to an emergency department	5.7%	Dartnell et al. [2]
Hospital admissions associated with drug-related problems among children	3.4%	Easton et al. [3]
Hospital admission caused by ADRs	3.2%	Pouyanne et al. [4]
ADR-related hospitalization of the residents at a nursing facility (during 4 years)	15.7%	Cooper [5]
Patients with ADRs as reason for hospital admission	7.2%	Lagnaoui et al. [8]
ADRs in hospitalized patients		
Serious ADRs in hospitalized patients	6.7%	Lazarou et al. [6]
ADRs during hospitalization in a cancer institute	5%	Lapeyere-Mestre et al. [7]
Number of ADRs per 1000 patient-days in a medical ward	10.1 cases	Lagnaoui et al. [8]
Number of ADRs per 1000 patient-days in a internal medicine department	5.6 cases	Moore et al. [9]

Legend: The percentages in the table either provide a measure of the proportion experiencing an ADR at a particular time point (prevalence) or the number of new ADRs in population over a period of time (incidence).

According to the literature a relevant proportion – ranging from 30% to 80% - of ADRs are judged to be preventable. A meta-analysis of 12 studies conducted by Beijer *et al.* showed that 407 of 1,410 patients (29%) were hospitalised due to ADRs, which were regarded as preventable.[4] The remaining hospital admissions were regarded as not preventable, e.g. a hospitalisation caused by anti-cancer cytotoxics was considered as unavoidable. Several activities were proposed to remedy against unnecessary hospital admissions: improve physicians' judgement and decision on the prescription, improve the patient compliance, improve communication with the patient or automate the signalling of risk events to improve surveillance results.

Cost Quantification

The measurement of the costs of those ADRs that caused a death or led to hospitalisation is the most straightforward. It is also possible from the description of the nature of adverse reactions to get some information about the severity of the effects and make cost estimations. However, it is not possible to identify, for example, the medical expenditures or number of days lost from work due to all kinds of ADRs.

a) The incidence of adverse drug effects during hospitalisation is reportedly high (2.1–6.5% of hospitalised patients, depending on source). Apart from the health implications of these effects for the patient, the cost to the hospital for a single ADR ranges between €2284 and €3093 (year 2000 values).

[3] Jonas Lundkvist, Bengt Jonsson: Pharmacoeconomics of adverse drug reactions. Fundamental & Clinical Pharmacology 18 275–280, 2004.

[4] Beijer H.J.M. and. de Blaey C.J: Hospitalisations caused by adverse drug reactions (ADR): a meta-analysis of observational studies. Pharm World Sci; 24(2): 46-54, 2002.

Table 2 Cost of prolonged hospitalisation due to ADRs

Total EU patient-days	564,423,331	*2005 data*
Prolonged hospitalisation due to ADR	3,160,771	*Conservative estimate 5.6 ADR per 1000PD (Moore et al.)*
Total cost of prolonged hospitalisation	€ 7,219,200,169	*Conservative estimate € 2284 EUR per ADR*
Cost of preventable ADR's	**€ 2,165,760,051**	*Conservative estimate: 30% of all ADR*

b) Hospital admissions due to ADR are an important part of the ADR burden. Assuming that approximately 3-7% of all hospital admissions are attributable to ADR this illustrates the enormous direct and indirect social and economic costs for a society.

Table 3 Cost of preventable hospital admissions due to ADRs

Total hospital admissions in EU25	**83,991,567**	*2005 data*
Average length of hospitalisation in EU25	**6.72 days**	*2005 data*
Cost per hospitalisation	**€ 3,199**	*Guidelines*
Total EU25 expenditure on inpatient care	**€ 268,665,505,425**	
Admissions due to ADR	**2,679,331**	*Conservative estimate: 3.19%*
Costs of admissions due to ADR's	**€ 8,570,429,623**	
Preventable admissions due to ADR	**803,799**	*Conservative estimate: 30%*
Costs of public health burden of preventable admissions due to ADR's	**€ 2,571,128,887**	

c) The literature on ADR-related costs other than those caused by hospitalisation or prolonged hospitalisation is limited. Johnson and Bootman applied a conceptual model to calculate the cost of all drug-related morbidity and mortality by estimates from practicing pharmacists. The resulting cost varied from a conservative estimate of $30 billion to a worst-case estimate of $130 billion annually in the US. The result should, however, be viewed with caution as it was based on uncertain assumptions and included problems like untreated illnesses, inappropriate drug choices, over dosages and patient non-compliance. Therefore we have considered only the most conservative estimate, which extrapolated to the EU population and adjusted for the exchange rate would be €63.2 billion (of which **€18.96 billion** could be considered as **preventable**, once again using the most conservative estimate of 30% preventable).

Our estimates are fully in line with data published in the scientific literature. According to Goettler et al. 5.8% of all medical inpatient are hospitalised on average for 9 days due to an ADR, adding up to costs of about 1 billion DM (€511m) / year in Germany. As one third of the ADR-related hospital admission might possibly be avoided, they estimated the potential savings to be as high as 350 million DM (€179m) per year in 1995 Germany[5]. Taking into consideration that ADRs occur in outpatient and inpatient care, authors conclude that their estimate of the economic burden of ADRs based on direct costs is very conservative. Indirect and intangible costs of ADRs for a society are assumed to be much higher but cannot yet be estimated validly.

[5] Goettler M., Schnneweiss S. And Hasford J.:ADR Monitoring – Cost and benefit consideration. Pharmacoepidemiology and Drug safety, Vol. 6 Suppl. 3: 79-90 (1997).

In the UK a major study of hospital patients found that up to 6.5% of admissions were due to ADRs, three-quarters of which were judged preventable. Of those patients admitted with an ADR, 2.3% died as a result. An earlier systematic review found that ADRs were responsible for 7% of hospital admissions and an estimated one in 10 hospital bed days in the UK. Pirmohamed *et al* has estimated that the number and seriousness of ADRs in primary care might be equivalent to the hospital figures and in their study the estimated annual cost to the National Health Service (NHS) was £466 million (€706 million).[6]

Potential impact of strengthening EU pharmacovigilance

Many ADRs are caused by intrinsic characteristics of pharmaceutical substances or by behaviour which cannot be influenced by legislation or any other action at the EU level. Nevertheless there is a clear potential to reduce public health burden by enhancing the EU PhV system.

Some ADRs are unavoidable for example the suppression of the blood and immune system caused by certain anti-cancer drugs. However, it has been estimated that at least 30% of ADRs are preventable. Examples of the latter include ADRs that only occur when a medicine is used at high dose or when two medicines are used together. These situations can be avoided by knowing the side effects of medicines, knowing how medicines interact with each other and ensuring that users of medicines have easy access to this information, including through product labelling.

Nevertheless there is a clear potential to reduce public health burden by enhancing EU pharmacovigilance for example, if we can detect fatal adverse reactions more quickly, if EU-wide decisions on the labelling of medicines can be taken and implemented more quickly, if warnings not to prescribe a certain medicine to a certain at risk group of patients or not to prescribe together two medicines dangerous when combined, then we can save lives and reduce suffering. This can be monetised if we assume that strengthening of EU pharmacovigilance could prevent 1% (conservative scenario) or 10% (optimistic scenario) of avoidable ADRs.

Conclusions

This chapter has aimed to monetise the potential of public health burden reduction due to optimised PhV provision. Even considering that in each calculation the most conservative available reference was been used, the potential saving is estimated between €236 million annually in the conservative scenario and €2.3 billion annually in a more optimistic scenario. Similarly, applying the same assumptions and methodology, it has been estimated that the package of measures could prevent 591-5,910 deaths and avoid suffering of 8,038-80,379 patients by preventing hospital admissions due to ADRs.

Table 4 Potential reduction of direct societal economic burden related to ADRs in the Community

Total costs of preventable ADRs (a+b+c) per year	€ 23,696,888,938
ADR burden prevented by strengthened EU Pharmacovigilance	
Optimistic scenario (10% could be prevented)	€ 2,369,688,894
Conservative scenario (1% prevented)	€ 236,968,889

[6] Pirmohamed M. et al.: Adverse drug reactions as cause of admission to hospital: prospective analysis of 18 820 patients. BMJ. July 3; 329(7456): 15–19

Studies regarding economic aspects of ADRs and preventability of ADRs have a number of methodological shortcomings. Nevertheless the literature provides clear evidence, that at a time when much emphasis is put on the containment of health expenses, there is a domain where, by investing in prevention, expense cutting could be done, while increasing quality of care.

2. Overview of industry resources deployed in Pharmacovigilance

Safety and efficacy profiles of newly launched drugs are based on the experiences of up to several thousand people in controlled clinical trials. At this level of exposure, however, clinical trials do not detect events that occur in as few as one patient per thousand. Likewise, important interactions with other drugs and medical conditions might go undetected. Thus, the public relies on post-authorisation surveillance to detect rare and unexpected reactions to new medications. The primary post-authorisation method for detecting signals of adverse drug reactions is a system of spontaneous reporting. In the EU, when an adverse drug event occurs and is recognised, the health care professional may report it directly to the respective national medicines agency or to the marketing authorisation holder, which is then required by law to submit the data to authorities within a specific time frame.

Overview of pharmaceutical companies' post-authorisation safety activities:

a) Pharmacovigilance department operations, including quality assurance, technology support, and training of staff;

b) handling of adverse drug reaction cases reported - **Individual Safety Case Reports** - after approval, including collection, scientific analysis, data entry into computer databases, medical review, follow-up, and reporting to worldwide regulators;

c) summary report production of aggregate postapproval adverse reactions information, including **Periodic Safety Update Reports**;

d) safety surveillance activities, including those related to postapproval **risk management**, safety-related product quality complaints, including product recall for safety reasons, responses to safety questions from worldwide regulators, literature review for adverse-event information, and provision of safety information to health care professionals;

e) **Post-Authorisation Safety Studies** including safety-focused epidemiologic activities;

f) activities required for safety-related **labelling changes** (excluding labelling changes for other reasons); and

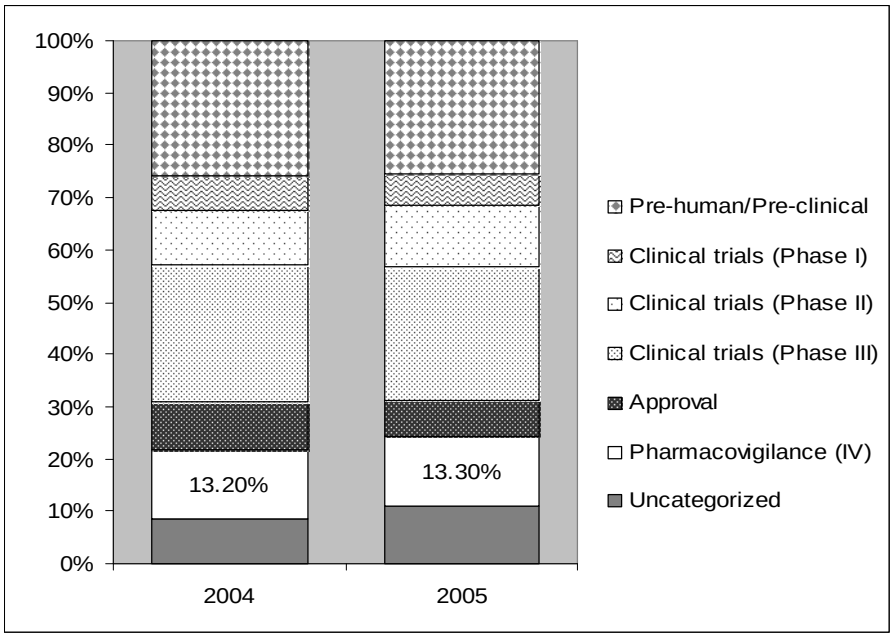
g) Ensure the authorities have up to date **oversight** of these activities.

Following signal detection and analysis, the MAH continues vigilance. Further actions taken by the manufacturer can include initiating new research, revising product labelling, submitting aggregated summary safety reports, writing a "Dear Health Professional" letter, instituting a risk management program, or withdrawing the product. Potential regulatory actions include recommending that the manufacturer conduct new research, requiring the manufacturer to re-label the product or write a "Dear Health Professional" letter, or withdrawing product approval.

Despite concerns about the adequacy of current methods of drug safety surveillance, there are only limited data available quantifying the total resources devoted by companies to post approval safety of their medicines. These suggest that only a relatively low proportion of industry research and development investments are devoted to PhV activities (see Figure 1). According to the Eurostat data 3700 companies were involved in production of

pharmaceutical preparation in the EEA in 2005 with a total turnover of €169.5 billion (€45.8 million per company). Taking into consideration a positive EU-25 trade balance of €28.8 billion in the area of medicinal and pharmaceutical products in the same year, volume of the Community pharmaceutical market can be estimated at €140.7 billion.

Figure 1 Structure of R&D costs in the innovative pharmaceutical companies



Source: PhRMA, Annual Membership Survey 2006

Methodology

Within the framework of the Assessment of the EU Pharmacovigilance system assessment, DG ENTR of the European Commission, in collaboration with EFPIA[7], EGA[8] and AESGP[9], conducted a questionnaire survey of the resources (financial, human and technological) deployed by European pharmaceutical industry in pharmacovigilance in 2005. The data were collected particularly in order to assess the economic burden of current EU pharmacovigilance requirements on companies.

For the purpose of the study the costs deployed in order to comply with the legal pharmacovigilance requirements for the EEA, consisting, at the time, of the 25 EU Member States and Norway, Iceland and Lichtenstein were considered. Only costs related to products already authorised were considered (and not products in development). Whether the work to satisfy the EU requirements is carried in the Community or not (e.g. PSUR prepared in the USA for submission in the EU) did not affect its inclusion in the figures. All financial data were asked presented in € and all data on human resource in full time equivalents (FTEs).

The Commission services received 83 anonymisedanonymous survey responses: 9 through AEGSP, 29 through EFPIA and 45 through EGA (see table 5 for more details). These were assigned a unique ID and all answers were, following their consistency and validity check, recorded in an Excel database. From 83 of the companies that responded to the questionnaire, 60 companies operated globally (73.2%), 11 only within the EU (13.4%) and 11 just in one EU country (1 missing value). In summary collected responses represent pharmaceutical

[7] EFPIA – European Federation of Pharmaceutical Industries and Associations. This Federation comprise 30 national pharmaceutical industry associations and 43 leading pharmaceuticals companies (http://www.efpia.org/Content/Default.asp).
[8] EGA – European Generic Medicines Association. This Association comprise 39 companies and 15 Associations (http://www.egagenerics.com/ega-links.htm)
[9] AESGP – European Self-Medication Industry. This Association comprise 26 national pharmaceutical industry associations (http://www.aesgp.be/aboutUs/objectives.asp)

companies holding marketing authorisations in total for more than 4,000 substances, with a global turnover of responding companies was more than €192.5 billion (only 70 of 83 companies provided data on turnover). However, at the same time 28 of the responding companies fulfilled the criteria for small and medium enterprises.

Table 5 Sample characteristics (aggregates for industry association)

Received via	Responses	Total number of authorised products	Turnover global*(€)
AESGP	9	298	1.714.381.000
EFPIA	29	1,215	168.913.520.714
EGA	45	2,717	21.909.680.891
Total	**83**	**4230**	**192,537,582,605**

**n=70 (67figures on global and 3on EU turnover)*

The questionnaire consisted of a total of twenty questions. For twelve questions responders were asked to choose one from pre-defined ranges rather than provide a numeric value. In order to quantify these responses, the median within the range was used for quantitative analysis (e.g. 3 for the range 1-5). Moreover bottom (minimum) and upper range (maximum) were considered for sensitivity analysis and confidence interval estimates.

Additional data

In February 2008, there was a series of roundtable meetings with the industry experts organised by the Commission services, in collaboration with the EU industry associations, with the aim of collecting additional in-depth information in order to better interpret data collected through the questionnaires and to quantify administrative burden cost of individual reporting obligations. Responding companies were asked to provide data at a more detailed level, broken down per individual operation where they had such data available or they could be reliably estimated.

The collected data were supplemented by an extensive literature search. Particularly results of the web-based survey conducted by Ridley et al.[10] provide additional information, although covering only one specific industry segment. In 2004 Ridley et al. sent survey questionnaires to twenty-five large drug manufacturers; in general, the largest of the large responded. The eleven companies that responded accounted for 71% of 2003 U.S. sales by the top twenty manufacturers.

Overall results of the Commission questionnaire survey

From eighty three reporting companies, within the EU,:

- Ø 16 employed in total less than 100 employees (20%),
- Ø 30 employed in total from 100 to 1,000 employees (37.5%),
- Ø 25 employed in total 1001-10,000 employees (31.2%, all but 3 operating globally) and
- Ø 9 employed in total over 10,000 employees (11.2%, all of them operating globally).

The results of the survey suggest that most of the companies are conducting their PhV function mainly in house except for a few smaller companies. On the other hand the largest companies often locate their main PhV activities partially or fully outside the EU.

[10] Ridley DB, Kramer JM, Tilson HH: Spending On Postapproval Drug Safety. Health Affairs 2006 (Vol. 25, Num. 2)

Table 6 Organisation of the company PhV system according to the company size

Company's pharmacovigilance function is located:				
	EU mainly	**Global**	**Outside the EU**	Companies total
In house completely	34	10	10	**54**
Employees total (average)	*4,990*	*18,910*	*28,810*	
In house mainly	17	5	2	**24**
Employees total (average)	*8,644*	*13,420*	*55,000*	
Outsourced completely	2			**2**
Employees total (average)	*300*			
Outsourced mainly	3			**3**
Employees total (average)	*383*			
	56	**15**	**12**	**83**

Three responding companies estimated their total annual cost of meeting the EU pharmacovigilance requirements at over 50 million € (all of them operating globally and employing more than 10,000 employees in total within the EU). Similarly another 3 companies, which spend on PhV function over 10 million €, are operating globally. On the other hand only one of 21 companies spending on pharmacovigilance over 1 million € is operating solely in the EU. All seven companies (8.7%) reporting their annual pharmacovigilance cost less than 1000€, have more than 100 employees (see table 7).

Within the sample of sixty companies that provided data both on their annual EU turnover and their EU PhV cost, their annual cost of meeting the EU pharmacovigilance requirements represented in total 0.59% of their turnover, with a median value of 0.19% (interquartile range 0.06%-0.48%). Seven companies spent more then 1% of their annual EU turnover on pharmacovigilance functions. These figures are in the same order of magnitude as the results presented by Ridley *et al.* estimating post-approval safety costs of large multinational companies at an average of $56 million for postapproval safety in 2003 (0.3 percent of sales), with nearly 70 percent of this cost dedicated to personnel.

The DG ENTR survey covered a representative sample of the pharmaceutical industry with an estimated total EU turnover of € 59.0 billion (42% of the EU market). Using Eurostat data on the total EU turnover for the pharmaceutical industry of €140.7 billion (2005 data), and extrapolating from the turnover data provided in the 2005/6 survey, the total EU industry annual industry resources deployed to meet the EU PhV requirements (scientific+administrative) can be estimated at €832.7 million (with a lower and upper range of €555.3 and €1124.3 million respectively).

Table 7 Total annual cost of meeting the EU pharmacovigilance requirements according to the company size *(as measured by number of employees within the EU)*

Employees within EU	Pharmacovigilance costs (€)	Number of companies
Less than 100	1001 – 10,000	3
	10,001 – 100,000	8
	100,001 – 500,000	1
	500,001 – 1 000,000	2
100 – 1000	Less than 1000	7
	1001 – 10,000	3
	10,001 – 100,000	12
	100,001 – 500,000	6
	500,001 – 1 000,000	2
1001 – 10,000	1001 – 10,000	1
	10,001 – 100,000	3
	100,001 – 500,000	3
	500,001 – 1 000,000	4
	1,000,000 - 5,000,000	10
	5 000,001 – 10 000,000	2
	10,000,000 - 50,000,000	1
10,001 – 100,000	500,001 – 1 000,000	1
	1,000,000 - 5,000,000	1
	5 000,001 – 10 000,000	2
	10,000,000 - 50,000,000	2
	More than 50 000,000	3

Table 8 Link between annual cost of meeting the EU pharmacovigilance requirements according to the company size and total number of staff deployed

Staff (FTEs) deployed to meet the EU pharmacovigilance requirements	Pharmacovigilance costs (€)	Number of companies
Less than 1	Less than 1000	1
	10,001 – 100,000	3
1 – 5	Less than 1000	8
	1001 – 10,000	7
	10,001 – 100,000	19
	100,001 – 500,000	10
	500,001 – 1 000,000	1
6 – 10	500,001 – 1 000,000	2
11 – 100	10,001 – 100,000	1
	100,001 – 500,000	1
	500,001 – 1 000,000	6
	1,000,000 - 5,000,000	11
	5 000,001 – 10 000,000	2
	10,000,000 - 50,000,000	1
	More than 50 000,000	1
101 – 1000	5 000,001 – 10 000,000	2
	10,000,000 - 50,000,000	2
	More than 50 000,000	1
1001 – 10,000	More than 50 000,000	1

From the point of view of human resources, 57% of companies employ 1-5 persons (full time equivalents) to meet the EU pharmacovigilance requirements, in particular 17 of 22 (78%) companies operating solely in Europe. Thereafter 29% of companies employ 11-100 FTEs.

Five companies, all of them from the innovative sector and operating globally reported more than one hundred employees in the PhV sector and one even more than one thousand employees. The study of Ridley *et al*. indicated the number of FTEs directed at postapproval safety ranged from 38 to 550 (mean [standard deviation], 298 [159.1]) per company and observed that companies with the fewest FTEs also have the fewest initial adverse-event reports and the lowest sales in the sample. On average, 57 percent of costs for FTEs were attributed to "staff qualified in a health disciplines" and scientists. The remaining FTE costs were for management and other staff, including data management.

Key pharmacovigilance activities

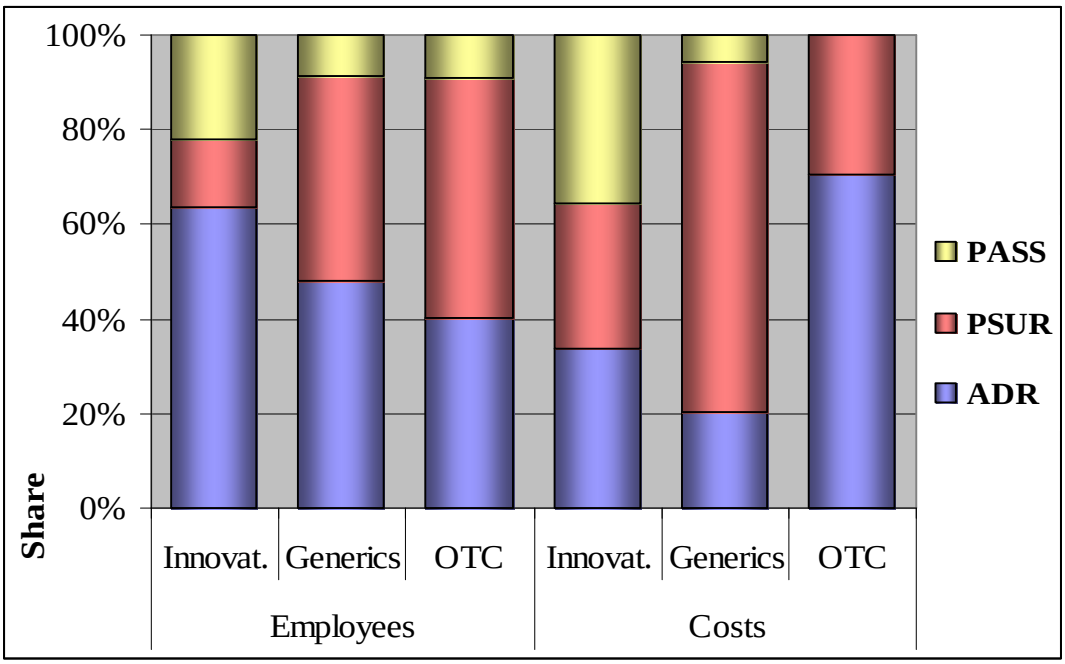
Available data indicate that most industry resource is devoted to three main activities:

Expedited ADR reporting - Collection, management and reporting of Adverse Drug Reaction (ADR) Single Case Safety Reports (ISCR).

Periodic Safety Update Reports (PSUR) - Production and submission within legally defined periods of summary reports of aggregate adverse reactions information.

Post-authorisation safety studies (PASS) - interventional or non-interventional studies on the safety of a medicinal product.

Figure 2 Commission questionnaire survey: Structure of deployed PhV resources per activity and industry segment



In summary:	**ADR** Reporting	**PSURs**	**PASSs**	**Total resources**
Employees	5,793	1,612	2,061	**9,466**
Costs	€ 299,006,680	€ 176,790,759	€ 356,903,781	**€ 832,701,221**

European pharmaceutical industry consists of three basic segments:

- Innovative companies (including biotechnologies) producing new molecules;
- Generic companies producing off-patent products and
- OTC companies focused on medicines available without medical prescription.

Figure 2 clearly illustrates the different nature of PhV operations in individual industry segments. While innovative companies, with a generally higher PhV cost, invest substantial resources to post-authorisation safety studies of their novel products, generic companies are mostly focused on periodic safety reporting. This also indicates the diverse impact of the proposed options on particular industry segments.

Expedited ADR reporting

The current ADR reporting rules are complex and lead to unnecessary duplication of reporting. For instance, reporting to the authorities' case reports of adverse reactions from the worldwide medical and scientific literature is currently an obligation on all companies leading to the same literature case report for generic medicinal products being submitted to multiple authorities by sometimes hundreds of companies.

Table 9 Human and financial resources deployed by companies on expedited ADR reporting (Number of companies per category)

Cost (€) / Staff (FTE)	Less than 1	1 – 5	6 – 10	11 – 100	101 – 1000
Less than 100€	3	3		1	
101 - 1000	3	3			
1001 – 10,000	4	7			
10,001 – 100,000	6	14	2		
100,001 – 500,000		8	2	2	
500,001 – 1 000,000		1	2	3	
1,000,000 - 5,000,000				5	
5 000,001 – 10 000,000				3	1
10,000,000 - 50,000,000					2
More than €50 000,000					1

Within the framework of the industry roundtables companies were asked to estimate the number of ADR reports managed each year that would qualify for expedited notification under the proposed new legislation and if possible, split in terms of serious ADRs (from all countries world-wide) and non-serious ADRs (EU origin), as per the proposed legislation. An average cost of one ADR report was estimated at €200-400 by industry experts and more than 30,000 unique reports are being processed a year by large companies (this corresponds to more than €6 million per 1 company). Based on data provided by individual companies (given in Table 10) the median savings from the proposals or the industry was estimated at 25.8%.

Table 10 Estimated savings due to rationalised ADR reporting (supplied by individual companies)

	Company A	**Company B**	**Company C**	**Company D**	**Company E**
Reports per year	22,724	31,500	6,900	11,000	11,525
Cost per report	€ 189	€ 200	€ 500	€ 150	€ 450
Current annual costs ('000 €)	4,295	6,300	3,450	1,650	5,186
Estimated savings ('000 €)	1,110	531	1,380	880	1,164
Costs saved	**25.8%**	**8.4%**	**40.0%**	**53.3%**	**22.4%**

Considering that the total resources deployed by the industry sector on ADR reporting were extrapolated to €299.0 million and using the median estimated saving of 25.8%, the savings due to rationalisation of the system are estimated at **€77.1 million per year** for the entire industry sector.

Periodic Safety Update Reports (PSUR)

Periodic safety update reports (PSURs) are the periodic reports that the MAHs have to submit to the concerned agencies containing the ICSRs they have received in the last period as well as other safety-relevant information such as new clinical trial data.

Table 11 suggests a relatively consistent pattern between resources deployed by the various industry segments as current legal provision place similar reporting requirements on all products whatever the risk posed (due to limited correlation between risk and reporting requirements). Eleven companies are partially or fully outsourcing preparation of PSURs.

Table 11 Human and financial resources deployed on PSUR (Number of companies per category)

Cost (€) / Staff (FTE)	Less than 1	1 – 5	6 – 10	11 – 100
less than €100	1	4		1
101 - 1000	1	5		
1001 – 10,000	5	8		
10,001 – 100,000	5	14	3	2
100,001 – 500,000		8	5	
500,001 – 1 000,000			4	3
1,000,000 - 5,000,000				5
5 000,001 – 10 000,000				1
10,000,000 - 50,000,000		1		
More than 50 000,000				1

The cost to prepare a single PSUR differs according to the incidence of reporting of adverse reactions related to the substance:

PSUR size:	Time to prepare:	Cost
Small PSUR -	76 hours -	€ 6000
Medium PSUR -	173 hours -	€ 14000
Large PSUR -	362 hours -	€ 28000

(data provided by the industry)

If we use the current informal work sharing between the authorities as a guide to the effects of the legal proposals, there would be major cost savings for industry and national regulators by reducing duplication of effort, particularly for generic companies due to major reduction in drafting of PSURs. The data provided by pharmaceutical companies suggest reduction of their submission of between 10 and 100% (depending on the company category). While the proposed reduction will not significantly affect innovative medicines with evolving risk/benefit profile, representing about 10% of marketed products, it is estimated that frequency of PSUR submission for well established products could halved (assuming average submission frequency 6-yearly instead of 3-yearly currently). On this basis, the saved resource per industry, mainly generic and OTC producers, is estimated at 38% of the current cost (as these PSURs are usually smaller), what corresponds to an estimated saving of **€68.2 million** for the entire industry sector **per year**.

In addition the Commission proposal will further reduce administrative burden by introduction of a single electronic submission to the EMEA. If we assume that the mean

number of versions of one PSUR in the EU is 13 (PhVWP data) then this additional reduction in workload for industry is substantial. Figures in Table 12 gives costs related directly to administrative tasks related to the submission of the reports to the authorities. Estimated saving of **€3.7 million** (for the entire sector) does not include savings resulting from preparation of one PSUR in a single format to all Member States at the same time.

Table 12 Industry savings resulting from centralised submission and worksharing

Total cost to MAH of 1 PSUR submission to 30 countries:	€ 7,000
Cost of submission to EU PhV committee only:	€ 250
Savings per 1 PSUR	€ 6,750
Estimated number of unique PSUR's per annum	550
Potential savings for the EU industry:	**€ 3,712,500**

Post-authorisation safety studies (PASS)

The collection and management of routine data (ICSRs and PSURs) represents key pharmacovigilance activities. There does, however, appear to be consensus that some information is not accessible from spontaneous reporting systems, such as long-term effects of medication, reliable comparisons between products and frequency of adverse effects. Although spontaneous reporting can assist in signal detection for rare cases of severe toxicity, it is less effective in detecting adverse events that are commonly manifest in the population. Post authorisation safety studies, either clinical trials or non-interventional epidemiological studies are conducted to fill these data and knowledge gaps. These studies can also be used to monitor the effectiveness of risk minimisation measures. PASSs and other data that can supplement the routine data (ICSRs and PSURs) have played a decisive role in recent safety issues.

Table 13 Number of PASS conducted by individual companies and their costs (Number of companies per category)

Cost (€) / PASS (n)	Less than 1	1 – 2	3 – 5	6 – 10	11 – 20	21 - 100
Less than €100	35			1		
101 - 1000	2	1				
1001 – 10,000	3	1	1			
10,001 – 100,000	1	3	1		1	
100,001 – 500,000	1	5			1	1
500,001 – 1 000,000		2	1	1		1
1,000,001 – 5,000,000			2		1	
10,000,000 - 50,000,000			1	1	1	
More than 50 000,000						1
Total	40	14	6	3	4	3

According to the results of the survey only 30 of 83 companies are conducting Post-authorisation safety studies (see Table 13). The costs of individual studies varies dramatically from €10,000 for a basic epidemiological study to more than €1 million for an international patient registry (e.g. Antiretroviral Drug Pregnancy Registry maintained by a consortium of companies) Although a number of generic companies is conducting a rather high number of PASS, innovative companies tend to deploy more resources in this area.
According to the survey the industry currently spends €356.9 million (with a lower and upper range of €202.0 and €511.8 million respectively) on post authorisation safety studies. The

proposals for a clearer legal basis for risk management plans and post-authorisation safety studies (including oversight) is difficult to quantify as it is dependent on the medicines brought to market each year (i.e. the products of industry research and development) and the known and suspected risks of these products as judged by the industry and the regulators. It is considered likely that there will be a decrease in poor quality studies including studies which have a promotional rather than safety aim and an increase in high quality safety studies including clinical trials and epidemiological studies. Taken together we can predict a maximum additional cost for industry of € 89.2 million representing an increased spending on post-authorisation safety studies of 25%.

Summary of the impacts on industry

Table 14 summarises the impact of the proposal on the industry. Proposed simplification measures would free up €244.3 million, comprising 29.3% of current industry costs. The cost savings would be particularly focused on SMEs producing old established products (notably the PSUR simplification) while all simplification would proportionally help SMEs the most. Part of these saving would be diverted into risk minimisation measures and more proactive data collection, particularly Post-authorisation safety studies. The total balance of the quantified impact is positive, resulting in **savings of €145.2 million** for the industry sector per year.

Table 14 Summary of economic impacts on industry

Options	Potential annual cost increase	Potential annual savings
Company Pharmacovigilance System Master File		€ 85,900,000
Clear legal basis for risk management plans	€ 89,225,945	
ADR Reporting simplification		€ 77,143,723
Literature screening by the EMEA		€ 10,000,000
Removal of routine requirement for PSUR+Worksharing		€ 71,953,732
Increase in fees payable to EMEA	€ 10,596,000	
Total	€ 99,821,945	**€ 244,997,456.49**

Table 15 Standard Costs model presentation of the industry costs

Insert here the name and reference of the regulatory act assessed						Tariff (€ per hour)		TIme (hour)		Price (per action or equip)	Freq (per year)	Nbr of entities	Total nbr of actions	Total cost
If the act assessed is the transposition of an act adopted at another level, insert here the name and reference of that 'original' act														
No.	Ass. Art.	Orig. Art.	Type of obligation	Description of required action(s)	Target group	i	e	i	e					
9	**Savings of changing the PV system**	Fees CP	Other	Other	CAP					72,800.0	2	125	250	18,200,000
10		Fees MRP	Other	Other	MRP					50,000.0	2	677	1,354	67,700,000
11	**Savings from ADR simplification reporting**		Submission of (recurring) reports	Filing forms and tables	model company					48.8	22,724	41	934,326	77,143,724
13	**Savings from literature scanning**	Internal	Information labelling for third parties	Retrieving relevant information from existing data	3 FTE	35		1,760		61,600.0	1	31	31	1,931,438
14		external	Information labelling for third parties	Retrieving relevant information from existing data	external literature screening company					412,000.0			0	4,306,020
15		data entry	Information labelling for third parties	Submitting the information (sending it to the designated recipient)	64 products					450.0			8,361	3,762,542
16	**PSURs**		Information labelling for third parties	Retrieving relevant information from existing data	generic and OTC					0.0	1	7,650	7,650	68,241,233
17			Submission of (recurring) reports	Submission of (recurring) reports	all companies					6,750.0	1	550	550	3,712,500

Total administrative costs (€) **244,997,456**

3. Overview of regulatory resources deployed in Pharmacovigilance

National Medicines Agencies

The Commission sponsored Independent study, as well as a survey conducted by the Heads of Medicines Agencies have presented data on the number of staff working in the regulatory authorities on pharmacovigilance.

The tasks covered include: data collection and entry, data management, risk assessment, regulatory action, risk communication, audit and quality assurance (QA) and monitoring of compliance. The staff profiles include medical doctors, pharmacists, scientists, administrative support and others. Table 16 provides an outline of available human resource in the EAA national medicine agencies and EMEA in 2004 and illustrates that only a relatively small part of the agency's resources are directly dedicated to PhV. The median proportion of PhV staff is only 5% of the total agency staff. About two-thirds of the PhV staff was devoted to scientific tasks.

Table 16 Resources of the EEA medicines agencies deployed in Pharmacovigilance

Variable	Total for 30 NCA's	Mini mum	25% quartile	*Average*	*Median*	75% quartile	Maxi mum
Staff total Agency	7,026	8.5	118.3	*270.2*	*170.0*	294.0	1452.0
PhV staff total	**317**	**1.0**	**2.8**	***11.8***	***6.3***	**11.8**	**68.5**
PhV staff administrative	116	0.0	1.0	*4.5*	*2.3*	3.5	45.5
PhV staff scientific	201	0.5	1.6	*8.0*	*5.0*	9.6	43.7
PhV staff pharmaceutical	71	0.0	1.0	*3.2*	*2.0*	4.1	12.0
PhV staff medical	72	0.1	1.0	*3.5*	*2.0*	4.4	13.5
PhV staff other	41	0.0	1.0	*5.2*	*1.0*	1.0	34.2
Per function:							
Persons Data coll./entry	127	1.0	2.0	*4.9*	*3.0*	5.0	30.0
Persons Data management	98	1.0	2.0	*3.9*	*2.0*	4.3	25.0
Persons Risk assessment	135	1.0	2.0	*5.4*	*3.0*	6.3	22.0
Persons Regulatory action	156	1.0	2.0	*6.0*	*4.0*	5.8	45.0
Pers. Risk communication	124	1.0	2.0	*4.8*	*3.0*	4.8	22.0
Persons Audit and QA	49	0.0	0.0	*2.2*	*1.0*	2.0	19.0
Pers. Monitor.compliance	46	0.0	1.0	*2.1*	*1.3*	2.0	8.0

All values expressed in Full Time Equivalents (FTE). Source: Fraunhofer study, 2005

The independent study has concluded that not all EU agencies have sufficient staff to guarantee the compliance with the current legal framework. The independent study has suggested major under-resourcing by the Member States in terms of meeting the current pharmacovigilance requirements (independent of the proposals put forward under option 4 of this impact assessment). Specifically the independent study has recommended a minimum of 1.2 pharmacovigilance staff per 1 million population. At present 17 of the national agencies employ less than this number. If this recommendation was followed then the Community would have 562 staff to meet the current requirements rather than the 317 available in 2004. This increase of 77% would make a major impact on the safety of medicines independent of any legal proposals.

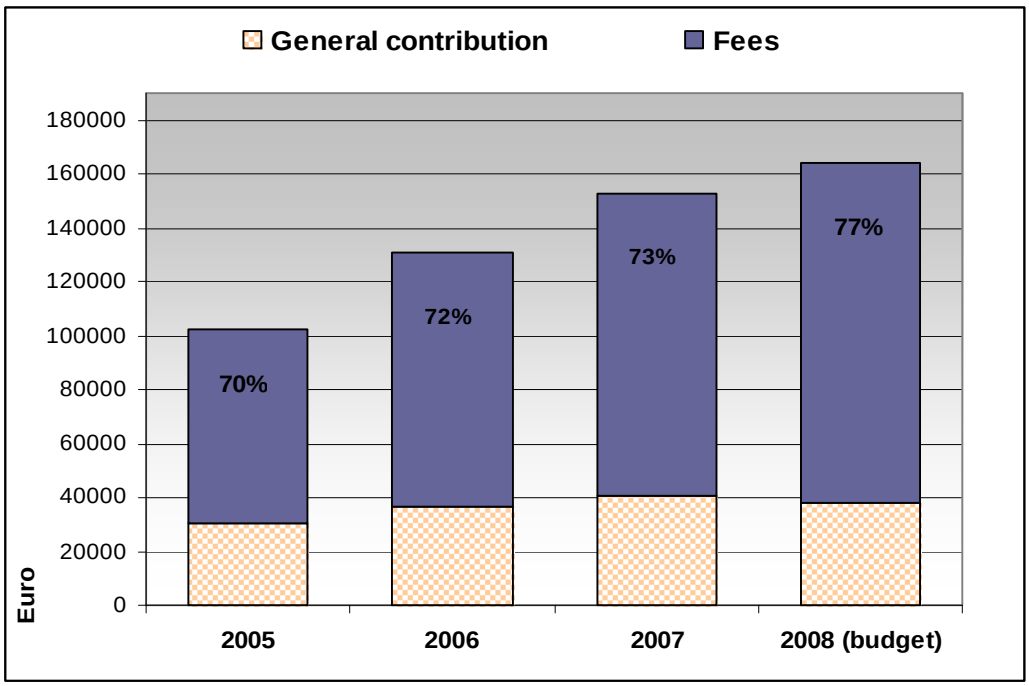
EMEA pharmacovigilance resources

The European Medicines Agency (EMEA) was created by Council Regulation (EEC) No 2309/93, which was replaced by Regulation (EC) No 726/2004 of 31 March 2004. The Agency operates through a network and coordinates the scientific resources made available by national authorities in order to ensure the evaluation and supervision of medicinal products for

human and veterinary health. The network gives the EMEA access to a pool of more than 4,000 experts participating in the work of the EMEA as members of the scientific committees, working parties, scientific advisory groups etc., covering the spectrum of activities of medicines regulation, of which pharmacovigilance is one.

The EMEA budget reached €163 million in 2007. An increase of the budget over the time was fully covered by the fees (estimated at 77% of total income in 2008), while the Community contribution remained stable over time. Fee revenues activities are estimated to further increase in the coming years in line with the general increase in centrally authorised products. Pharmacovigilance and maintenance activities accounted for 13.5% of the Agency human resource (ca. 70 FTEs) and 14.54% of the Agency costs (€ 25.2 million incl. support service) in 2007.

Figure 3: EMEA budget evolution 2005-2008



EMEA Pharmacovigilance activities (2007, EMEA Annual Report)

- The EMEA received 381,990 adverse drug reaction (ADR) reports in total in 2007- an increase more than 25% compared to the previous year. 40 % of ADR reports received related to centrally authorised medicinal products.
- The EMEA received 63,393 reports concern investigational medicines, i.e. adverse drug reactions observed during clinical trials. This is an increase of 18% compared to 2006.
- A total of 762 suspected signals concerning 139 intensively monitored products, and 349 suspected signals concerning 162 routinely-monitored products, were identified. Following further investigation, 22% (132) suspected signals required follow-up for intensively-monitored products, including involving the Rapporteur for 43 signals. About 10% (33) signals were followed-up for routinely-monitored products, with involvement of the Rapporteur in 21 cases.
- The Agency reviewed 92% of the Risk Management Plans (RMPs) submitted as part of new applications.
- The number of periodic safety update reviews conducted during 2007 (309) was 15 % higher than in 2006.

Impact of the Commission proposal on the EMEA resources

Cost to the EMEA of literature monitoring

On the basis of estimates from the EMEA (3 additional information analysts if the main function was outsourced) and from one private literature monitoring company11 (€533,333 annually for 3000 monitored substances, doubled to cover uncertainty relating to the number of substances and detailed processes), we can estimate the increase in costs to the EMEA of approximately €1.56 million per year.

Cost to the EMEA of the new PhV committee structure

It is considered that the amendments to the EMEA PhV committee structure (including replacement of the existing Working Party) would not lead to an increase in costs compared the existing costs. The committee structure upon which the Commission consulted publically in December 2007 would have lead to an increase of €472,308 compared to running the current working party. However, based on the feedback of stakeholders and in an attempt to reduce costs, the final proposal for the committee structure has been revised to include a small expert committee on PhV. This results in an overall neutral effect of the committee structure changes compared to the current situation.

Cost to the EMEA of the revised Community PhV referral

There is experience with the current Community referral system including the current increasing use of the specific PhV referral (Article 107 of Directive 2001/83/EC). Based on this experience and the increased clarity of what should be resolved at EU level that the new legal proposals will bring, it is considered that the number of referrals is likely to be in the range 10 to 30 per year. If we use the mid point of this range, and assuming the assessment/coordination costs to be equivalent to a Type II variation in the centralised procedure, this will represent a cost to the EMEA in payments to rapporteurs of 20 x €36,400 = €728,000 and income from fees of 20 x €72,800 = €1,46 million.

Cost to the EMEA of the revised transparency and communications provisions

Increased costs for EMEA, in comparison to resources already foreseen in the budgetary planning, would be required to support an increased level of transparency and the enhanced Community coordination of PhV communications. This is estimated at €646,832 on a yearly basis, covering 4.0 FTEs to manage the documents and the website (including dealing with confidentiality issues and one "communication manager" to formulate urgent safety communications). The one – off costs for transparency and communication (€ 1 Million) should be borne by fees (€ 500 000 in 2012 and 2013).

Cost to the EMEA of the Community oversight of non-interventional post-authorisation safety studies

The number of non-interventional post-authorisation safety studies (PASS) reported in the 2006 industry survey was 600 (after extrapolation) and assuming that 50% would be conducted in more than one Member State, we can then estimate the number of protocols to be scrutinised by the EU committee structure as 300 with a cost of €485,124, which comprises 3 FTEs for EMEA coordination and initial screening. Based on the fee estimates above these procedures would attract €1,830,000 in industry fees of which half would be paid to rapporteurs leaving €915,000 to the EMEA.

Cost to the EMEA of the Community oversight of risk management systems

The assessment of risk management systems takes place under the current legal framework. From a budget perspective the key addition from these legislative proposals will be new risk management systems for product already on the market i.e. assessments not linked to new

[11] Wolters Kluwer Health

marketing authorisation applications. The number of additional Community assessments of risk management systems is estimated to be 100 per year. Assuming the assessment/coordination costs to be equivalent to a renewal in the centralised procedure, this will represent a cost to the EMEA in payments to rapporteurs of 100 x €6,050 = €605,000 and income from fees of 100 x €12,100 = €1.2 million.

Additional cost to the EMEA from enhancements to the Community PhV database

The current EU Telematic Plan foresees development costs for the Community PhV database (Eudravigilance) independent to any change in legislation. Nevertheless the proposed changes including increased database access by stakeholders would require additional one-off development costs for human resources, hardware and software of an estimated €2,871,000 in total.

It should be noted that legislative proposals are unlikely to enter in to force until 2011 but that the database enhancements will need to be live at the time of entry into force as the proposed reporting systems rely on the Member States accessing the data via the Community pharmacovigilance database. Given that:

- Ø the existing EMEA telematics budget is of €74.1 millions for the six-years up to and including 2013,
- Ø the this existing EMEA telematics budget includes €8 million earmarked for the pharmacovigilance database (of which 3.7 millions is programmed before the expected entry into force of 2011),
- Ø the EMEA has been in budgetary surplus in recent years (e.g. €8 million in 2006),

EMEA should be able to re-programme the one-off €2.87 Million required for the Community pharmacovigilance database from its existing telematics budget (with or without subsidy from any budget surplus for 2008) and to request that the EMEA delivers the enhanced database functionality prior to the expected entry into force date of 2011.

Additional cost to the EMEA from running the collection and management of PhV data

Additional staff of 10 FTE for running the collection and management of PhV data in EudraVigilance from a business perspective (ADR processing) would bear an additional cost estimated at €1.62 million. This includes the handling of individual case safety reports, as well as activities related to the manual recoding of medicinal product information included in these reports.

Cost to the EMEA of Periodic Safety Update Report (PSUR) assessment work-sharing

We can then estimate the number of Periodic Safety Update Reports (PSURs) to be assessed by the EU committee structure as 1000 with a cost of € 485,124, which comprises 3 FTEs for EMEA coordination. Based on the fee estimates above these procedures would attract €6,100,000 in industry fees of which half would be paid to rapporteurs leaving €3,050,000 to the EMEA.

The calculations estimated a one-off increase of cost for EMEA of €3.9 million (setting up of the EU Safety Portal and enhancement of Eudravigilance functionality) and ongoing costs of €10.1 million annually, including payments to rapporteurs, 23 FTEs needed in addition to the current Agency staff dealing with pharmacovigilance (increase of 38% in the area of phramacovigilance), and just over €1 million annually for non-staff costs for literature monitoring. Table 17 indicates spread of major economic impacts on the EMEA over time.

Table 17 Major economic impacts on EU and national regulators (all values in Euro).

EMEA costs	Year 2011	Year 2012	Year 2013	Year 2014	Year 2015	Year 2016
One-off		500,000	500,000			
FTE	5	23	23	23	23	23
Salaries annually	808,540	3,719,284	3,719,284	3,719,284	3,719,284	3,719,284
Other annual costs.		1,066,667	1,066,667	1,066,667	1,066,667	1,066,667
Rapporteurship		5,298,000	5,298,000	5,298,000	5,298,000	5,298,000
Total costs	***808,540***	***10,583,951***	***10,583,951***	***10,083,951***	***10,083,951***	***10,083,951***
Income Fees	***0***	***10,596,000***	***10,596,000***	***10,596,000***	***10,596,000***	***10,596,000***
Balance	**-808,540**	**12,049**	**12,049**	**512,049**	**512,049**	**512,049**

Impact of the Commission proposal on the EU regulatory resources

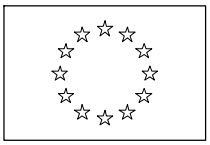
Table 18 summarises major economic impacts on the EU (EMEA) and national regulators (national competent authorities of 30 EEA Member States). Besides additional costs for the EMEA calculated in the previous section, a lesser overall cost increase was foreseen for NCAs, and this was estimated at an additional 54 FTEs corresponding to personnel costs of €4.7 million annually (this would be spread over 30 NCA's). In addition a one-off cost related to developing and linking their websites to the EU safety portal was estimated at €3 million across Member States.

Table 18 Major economic impacts on EU and national regulators (all values in Euro).

Analysed options (revised if applicable)	**EMEA**				**National competent authorities** (30)		
	One-off	Ongoing costs- annually			One-off	Ongoing- annually	
		FTE	Personal	Other		FTE	Costs
EU decision making				728,000			
Drug safety transparency and communication	1,000,000	4	646,832		3,000,000	27	2,328,480
Codification and oversight PASS		3	485,124	915,000		12	1,034,880
ADR Reporting simplif./ Eudravigilance	2,871,000*	10	1,617,080				
Literature screening by the EMEA		3	485,124	1,066,667			
Legal basis for patient's reporting						15	1,293,600
PSUR Assessment Worksharing		3	485,124	3,050,000			
Risk Management System assessment				605,000			
Total	**3,871,000**	**23**	**3,719,284**	**6,364,667**	**3,000,000**	**54**	**4,656,960**

**Re-programmed from existing telematics budget*

However the costs outlined above would not impact the EU budget. The legal proposals specifically foresee allowing the industry to be charged fees for the conduct of pharmacovigilance by the EMEA and national authorities. Regarding EMEA fees, given that the EMEA budget is currently in the surplus, whether an EMEA fee increase is necessary, and if the size of that increase will have to be judged at the time of entry into force of the new legislation.



COMMISSION OF THE EUROPEAN COMMUNITIES

Brussels, 17 September 2008

COMMISSION STAFF WORKING DOCUMENT

Annex 3 of the Report on the impact assessment of strengthening and rationalising EU Pharmacovigilance

EVOLUTION OF THE SPECIFIC POLICY OPTIONS

Selection specific policy option	Rejected alternative specific policy options	Rational for selection of specific policy option (based on qualitative impact analysis including stakeholder feedback)
Clarification and **codification of the tasks and responsibilities** of involved parties and **establish standards**	Maintain the status quo with most tasks, responsibilities and standards in guidelines	Ø As the current guidelines are not legally binding there is extensive non-compliance by the industry. Ø Absence of detail in legislation leads to divergent and additional administrative requirements from the Member States. Ø Absence of legal clarity leads to duplication of effort between different regulatory authorities.
Establishment of a **clear EMEA committee structure** for pharmacovigilance scientific assessment and decision making coordinating activities and making recommendations on the safety of medicines at the EU level. New small expert committee.	1. Maintain current informal EMEA Pharmacovigilance Working Party but make its outputs legally binding 2. Pharmacovigilance Committee with Member State representation	Ø For outputs to be legally binding the Committee making recommendations needs to have a legal identity. Ø Current Pharmacovigilance Working Party lacks certain necessary expertise. Ø No patient or healthcare professional representatives currently. Ø Member State representation may not maximise expertise. Ø Member State representation creates a large committee with high costs.
Rationalising the **EU referral procedures** for nationally authorised products with decision-making going through the Member State "Coordination Group" for issues only affecting nationally authorised products and the EMEA Committee for Human medicinal Products for referrals relevant to centrally authorised products	All pharmacovigilance issues assessed only by the new pharmacovigilance committee then subsequently by the current EMEA Committee for Human Medicinal Products. All referrals lead to a Commission decision	Ø Current Committee for Human Medicinal Products is already over-burdened. Ø Current Committee for Human Medicinal Products lack sufficient expertise. Ø Would result in a large number of Commission decisions. Ø Opportunity to maximise the use of the existing MS "Coordination Group"

Increasing drug safety **transparency** via establishment of an EU and National portals on the safety of medicines	Legislation to state which documents are made public but do not specify how	Ø Having all relevant medicines safety documents collated in one place will dramatically facilitate the ease with which stakeholders can find the relevant information. Ø Consistent methods will be applied by the Member States.
Improved EU **coordination of communication** about major new or changing safety issues with EMEA at the hub – Member States make best effort to follow key messages and distribution timetables	EMEA to be responsible for all communications on behalf of the Member States (requested by industry in consultation)	Ø Member State authorities are closest to their citizens and best place to distribute information to them Ø Member State authorities know the nuances of medical culture in their country Ø Use of all relevant languages facilitated by the Member State authorities being actively involved
Introduction of a new section on **'key information' in the product information** with a transitional implementation period	1. Present key safety information rather than benefit risk information 2. Immediate implementation of the changes to product information	Ø 1. The second public consultation proposed have key information on safety only as a risk minimisation tool. Stakeholders pointed out that highlighting / emphasising risks in isolation would lead to patients discontinuing their medicines i.e. being denied the positive effects of medicines. Ø 2. Stakeholders pointed out that guidance was needed to support implementation. Ø 3. Stakeholders pointed out that immediate implementation would create significant costs whereas staggered implementation over 5-years would create minimal costs as most product information would be updated during this time anyway.
Companies to maintain on site a "Pharmacovigilance System Master File" to ensure robust but un-bureaucratic **oversight of companies**	Maintenance of the "Pharmacovigilance System Master File" at the site of the EMEA with 'validation' by EMEA on behalf of the Community.	Ø Alternative would place a major additional administrative burden on the EMEA which was considered unnecessary given that the proposal includes provision for the files to

pharmacovigilance systems		submitted on request and viewed during inspections. Ø Subsidiarity would not be fully respected if the EMEA validated files for all nationally authorised products.
Provision of a clearer legal basis for **risk management plans** for new and authorised products with safety concerns, including post-authorisation safety studies	Risk management plans annexed in their entirety to the marketing authorisation rather than just key measures contained therein.	Ø The alternative option was the subject of public consultation however, stakeholders suggested that having all the detail of a risk management plan annexed to the MA and therefore legally binding would create legal uncertainty for companies.
Codification of guiding principles and oversight for the conduct of **non-interventional post-authorisation safety studies**	Limit the authorities objection criteria to studies being promotional or the study being a clinical trial.	Ø There was a clear call from stakeholders for oversight to ensure that studies have a scientific / public health objective.
Reporting of adverse drug reaction simplification using the EU Eudravigilance database as a central tool	1. Companies to report EU domestic cases to Eudravigilance and the country of origin. (suggested by some regulators). 2. Expedite (report within 15-days) non serious EU cases.	Ø 1. Duplicative reporting to the Member State is redundant if Eudravigilance makes reports fully available to the MSs and duplicative reporting is a major administrative burden on the industry. Ø 2. Major increase in workload for the industry of expediting all non-serious cases with minimal health benefit (indeed preventing the prioritisation of serious reports could lead to reduced quality data being submitted)
Scanning literature by the EMEA with a clearly defined in scope	EMEA to be responsible for all products authorised in the Community and for all literature.	Ø Major workload / burden for the EMEA. Ø Problem of duplicate reporting only exists for substances included in more than one product (i.e. mainly a problem for generics) Ø Industry wishes to closely monitor the literature for its new innovative products.
Exchange of data on medication errors	Create legal obligation for all medication	Ø Treaty basis is for the single marking in

that result in an adverse reaction including between the competent authorities for medicines and those for patient safety	errors to be reported to the authorities	medicinal products therefore it is appropriate to let member States put in place their own medication error reporting schemes with this legislation simply insuring that industry reports and that authorities exchange information received.
Provision of the **legal basis for patients to report suspected adverse drug reactions** directly to the national competent authorities	Reports sent by patients to companies who are responsible for data entry and forwarding reports to the authorities (to reduce the data entry burden on the authorities).	Ø Major objection from certain stakeholder groups (including Member State authorities) to having industry as the primary receiver of reports.
No routine requirement for industry periodic reports for low risk, old and established products	Maintain current requirements for periodic reports.	Ø Major burden from uncoordinated submission of reports including for very well established and low risk products. Ø Diverts resource away from monitoring the safety of higher risk products.
Provision of the legal basis for the new **EMEA pharmacovigilance committee structure to require submission and coordinate assessment of PSURs** and make consequent recommendations for product labeling	Maintain current informal work-sharing between the member State authorities	Ø Although the current informal work-sharing has increased the amount of synchronisation of submission of reports for products containing the same substances, companies do not have to comply and the outcome of assessments is frequently not implemented.