COMMISSION OF THE EUROPEAN COMMUNITIES

Brussels, 10.12.2008
SEC(2008) 2670
Volume I

COMMISSION STAFF WORKING DOCUMENT

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

IMPACT ASSESSMENT

{COM(2008) 664 final}
{COM(2008) 665 final}
{SEC(2008) 2671}

TABLE OF CONTENTS

TABLE OF FIGURES

LIST OF ABBREVIATIONS

ADE	Adverse Drug Event
ADR	Adverse Drug Reaction
AERS	Adverse Event Reporting System (USA)
CAP	Centrally Authorised medicinal Product
CHMP	Committee for Medicinal Products for Human Use
DG ENTR	Directorate-General Enterprise and Industry
EEA	European Economic Area
EMEA	European Medicines Agency
ERMS	European Risk Management Strategy
EU	European Union
FDA	Food and Drug Administration (USA)
Generics	Medicines containing the same active substance as the originator product after patent expiry
HCP	Healthcare Professional
HMA	Heads of EEA Medicines Agencies
IA	Impact Assessment
ICH	International Conference on Harmonisation of Technical Requirements
ICSR	Individual Case Safety Reports
MAH	Marketing Authorisation Holder
MedDRA	Medical Dictionary for Regulatory Affairs
MRP	Mutual Recognition Procedure; Mutual Recognition authorised Product
MS	EEA Member State
NAP	Nationally Authorised medicinal Product
NCA	National Competent Authority
OTC	"Over-the-counter" medicine, available without doctor prescription
PASS	Post-authorisation Safety Study
PIL	Patient Information leaflet
PhVWP	EMEA Pharmacovigilance Working Party
PhV	Pharmacovigilance
PSUR	Periodic Safety Update Report
R&D	Research & Development
RMP	Risk Management Plan
SCM	Standard Cost Model
SPC	Summary of Product Characteristics
Volume 9a	Current EU pharmacovigilance guideline
WHO	World Health Organisation

1. PROCEDURAL ISSUES AND CONSULTATION OF INTERESTED PARTIES

An adverse reaction to a medicine (drug) is a response to a medicine which is noxious and unintended. Pharmacovigilance is defined as the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem. It is a key public health function and comprises:

- Collecting and managing data on the safety of medicines
- Looking at the data to detect 'signals' (any new or changing safety issues)
- Evaluating the data and making decisions with regard to safety issues
- Acting to protect public health (including regulatory action), if necessary
- Communicating with stakeholders
- Audit, both of the outcomes of action taken and of the key processes involved.

Pharmacovigilance is fundamentally about reducing risks to citizens from adverse reactions to medicines.

Organisation and timing

The impact assessment process was started in 2004 when an external study was initiated to assess the EU Pharmacovigilance system. Assessment of 30 agencies (29 EEA national agencies – including two in Germany – and the EMEA) was particularly relevant at that time as the revised EU pharmaceutical legislation entered into force in late 2005 and 2004 brought 10 new Member States into the system.

The final report of the study entitled 'Assessment of the Community System of Pharmacovigilance' informed an extensive public consultation process launched in spring 2006.

A Commission inter-service steering group was established in February 2007 and has met four times. The Commission services participating were Health and Consumer Protection (SANCO), Research (RTD), Secretariat-General (SG) and Information Society and Media (INFSO). The project on Modernising Pharmacovigilance for Pharmaceuticals has been referenced in the Commission Agenda Planning as 2008/ENTR/003 (a Regulation amending Regulation (EC) 726/2004) and 2008/ENTR/019 (a Directive amending Directive 2001/83/EC).

Consultation and expertise

During the impact assessment process the Commission services extensively consulted all relevant stakeholders using the whole range of communication means.Two general web-based public consultations were supplemented by questionnaire surveys and workshops with specific stakeholder groups. The Commission Pharmaceutical Committee (made up of Member State representatives), the EMEA scientific committees (again having Member State representation), and the Heads of EEA Medicines Agencies (HMA), have been

regularly updated and consulted on progress of the initiative. Concurrently, comments of the Commission services raised during the inter-service steering group meetings were fully taken into consideration.

1.1.1. Independent study

The independent study "Assessment of the European Community System of Pharmacovigilance"[1] had three objectives: 1. document the current EU pharmacovigilance system; 2. identify its strengths and weaknesses, and; 3. make recommendations to strengthen the system. The study has a particular focus on the regulatory agencies. The national medicines agencies, as well as the EMEA were included in the research in several ways: structured interviews were conducted at each medicine agency and a written survey was carried out with representatives of the agencies' pharmacovigilance units (mainly the heads of departments), with representatives of industry associations and with healthcare professionals. Moreover, the HMA Facilitation Group for the "European Risk Management Strategy" (ERMS) and other experts were systematically involved in the execution of the study and the discussion of preliminary findings and conclusions. Finally, a stakeholder workshop was held by the independent researchers to gather views and orientations.

1.1.2. Public consultations

Details of the two halves of the public consultation are provided at Annex 1. Both were web-based public consultations, linked to the "Your Voice in Europe" website. The Commission services conducted the first part of the public consultation between 16 March 2006 and 12 May 2006. This was broad in scope seeking stakeholders' views on the strengths and weaknesses of the current EU system of pharmacovigilance and how the system could be strengthened. The Commission consultation received 48 contributions from all relevant stakeholder groups and results were made public at the DG ENTR website in February 2007[2]. The consultation response provided compelling arguments that the current system is over complex, that resources are not best used often being focused on meeting bureaucratic requirements rather than proactively gathering data and information about the safety and risks of medicines. There was a strong and clear demand from stakeholders for the Community pharmacovigilance system to be strengthened and rationalised. In February 2007, in response to the consultation outcome, Vice-President Verheugen announced the "Strategy to Better Protect Public Health by Strengthening and Rationalising EU Pharmacovigilance" comprising both better implementation of the current legal framework and proposals for enhancement of the legal framework.

The second part of the public consultation, conducted between 5 December 2007 and 1 February 2008, specifically addressed draft proposals for changes to EU legislation relevant to the safety of medicines. The consultation documents were also e-mailed to all those stakeholders who had submitted a response to the first part of the consultation in 2006. The second part of the consultation received 82 contributions from the range of relevant stakeholder groups.

---

[1] http://ec.europa.eu/enterprise/pharmaceuticals/pharmacovigilance_acs/docs/acs_consultation_final.pdf

[2] Complete results of public consultation are available at:
http://ec.europa.eu/enterprise/pharmaceuticals/pharmacovigilance_acs/index.htm

1.1.3. Targeted consultation

To facilitate the process of public consultation and impact assessment DG ENTR complemented the formal web-hosted public consultations described above by presentations to the scientific and policy committees of the European medicines regulatory network, dedicated workshops with key stakeholder groups, expert roundtable meetings and questionnaire surveys.

In addition to the means of consultation outlined above, various bilateral meetings with a number of interested parties were conducted in 2006-2008 on this project, to discuss the available policy options and their likely impact.

Questionnaire survey and roundtable meetings with industry experts

During 2006 The European Commission, in collaboration with the EU industry associations, conducted a survey of the resources (financial, human and technological) deployed in pharmacovigilance including those to meet EU regulatory requirements. A number of roundtable meetings with the industry experts were organised by DG ENTR in order to better interpret data collected through the questionnaires and to quantify administrative burden cost of individual reporting obligations.

Commission Impact Assessment Board

A draft of this Impact Assessment was reviewed in April 2008 by the independent Commission Impact Assessment Board (IAB). The Board issued its Opinion on 7 May 2008 and f found the draft Impact Assessment to be of generally good quality and noted the effort made at ensuring a proportionate level of analysis and the quantification and monetisation of costs and benefits. The IAB made a number of suggestions to improve the draft and these have been included in this final report. Of note, this final report:

- Links the identified problems to objectives and specific policy options and these are used consistently through the report and presented in a schema in Section 3.

- The process for identifying the 15-specific policy options is described and important steps in their evolution are presented. Key alternatives to the 15-specific policy options are presented in a new Annex 3.

- Provides additional explanation of: the effect of divergent Member State action, previous change to pharmacovigilance legislation, the lack of trust of patients, environmental impact and the use of soft-law in the pharmaceutical sector.

- Explains the legal strategy behind the rejection of the stakeholder call for a single pharmacovigilance regulation.

- Includes a presentation of industry costs in Annex 2 using the standard cost model.

- Includes some restructuring and presentation change to improve readability.

2. PROBLEM DEFINITION

What is the issue?

Medicines contribute considerably to the health of EU citizens. The discovery, development and effective use of medicines have improved many people's quality of life, reduced the need for surgical intervention and the length of time spent in hospital and saved many lives. Consumption of medicines is high and is increasing, with pharmaceutical market value reaching €196.5 billion (retail prices) in the EU in 2006.

Medicines research and development is a complex and strictly controlled process, which continues for many years. A marketing authorisation is granted by regulatory authorities only if, based on the information available at the time of approval, the benefits of a pharmaceutical product, when used as directed, are judged to outweigh the known risks in populations like those studied prior to approval. Pharmaceutical products are tested extensively in animal and other non-human (pre-clinical) studies before being given to humans in clinical trials. This rigorous process of pre-clinical and clinical testing demonstrates efficacy (i.e. that the medicine works), provides data on safety and eliminates many medicines with an unacceptable benefit-risk profile. After many years of research, there is a considerable amount of information that is provided to regulatory authorities. It is with these data that companies apply for marketing authorisations for medicines and regulators make decisions on granting such authorisations.

Despite the scientific strengths of the pre-marketing development and approval processes, no medicine on the market is without risk. It cannot be assured that all risks are known at the time a medicine first enters the market. Instead, it is likely that some risks will only become known after a medicine receives market approval. Scientific literature suggests that adverse drug reactions (ADR) represent the fifth most common cause of death and are responsible for about 3-10% of all admissions to hospitals in the EU. In addition to their impact on human health, adverse drug reactions (ADRs) also have significant impact on healthcare costs[3].

Pharmacovigilance is a system of post-marketing surveillance to evaluate the effects of medicines in normal clinical settings that entails collecting and analysing data, including reports of suspected adverse reaction to marketed medicines. The purpose of collecting and analysing the data are to detect new and changing safety patterns so that action can then be taken to reduce the risks to patients. Action might include warnings related to the newly identified risk, stopping those patients at most risk from receiving the medicine or even withdrawing the product. The most common action includes updating the product information (including the Patient Information Leaflet) so that patients and healthcare professionals are informed of the risks of the product and can make an informed choice about use the product.

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

2.1.1. Systems of pharmacovigilance in other countries

The independent study analysed the pharmacovigilance systems in the USA, Japan and Canada and concluded that the organisation of pharmacovigilance is broadly the same in these three countries with some aspects being fully harmonised through the International Conference on Harmonisation (ICH). More details of the comparative analysis can be found in the report of the independent study[4].

Current regulatory framework

In order to ensure the quality, safety and efficacy of medicines, a medicinal product may only be placed on the market in the Community when a marketing authorisation has been issued either by the competent authority of a Member State for its own territory or by the Commission when an authorisation is granted for the entire Community. A marketing authorisation for a medicinal product in more than one Member State must be applied for through one of three procedures: either the "Centralised Procedure", determined by Regulation (EC) No 726/2004[5], or the "Mutual Recognition Procedure" or the new "Decentralised Procedure", regulated by Directive 2001/83/EC[6]. In addition, national authorisations remain available for products to be marketed in one single Member State.

In addition to the legislation referred to in the previous paragraph, detailed guidelines, definitions, standards and information regarding the precise conduct of pharmacovigilance related procedures are to be found in a number of guidance documents, principally "Volume 9A of the rules governing medicinal products in the European Union – Pharmacovigilance"[7] and in the pharmacovigilance related guidelines of ICH. The basic legal texts are supplemented by Commission Regulation (EC) 1085/2003 and Commission Regulation (EC) 1084/2003 which describe the procedures that have to be followed in the case that an existing marketing authorisation of medicinal products on the European market has to be changed (the variations regulations), and by Commission Regulation (EEC) 540/95 that regulates the procedures concerning "suspected unexpected non serious adverse reactions".

It should be noted that EU legislation provides only high level principles for pharmacovigilance with the detailed procedures being left to Community guidance (principally Volume 9A of Eudralex). Furthermore, the high-level nature of the legislation leaves significant scope for Member State elaboration which has lead to divergent legal and administrative practices becoming established in the Member States (with significant administrative burden without necessarily added value in terms of health protection).

Who is affected, in what ways, and to what extent?

---

4 http://ec.europa.eu/enterprise/pharmaceuticals/pharmacovigilance_acs/docs/acs_consultation_final.pdf

5 Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency (Official Journal L 136, 30/4/2004 p. 1 - 33).

6 Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use (Official Journal L 311, 28/11/2001 p. 67 - 128) as amended by Directive 2002/98/EC, Directive 2004/24/EC and Directive 2004/27/EC.

7 http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/homev9.htm

2.1.2. Key stakeholders

The current EU pharmacovigilance system places legal obligations on the Member States (and their national competent authorities for medicines), the EMEA, the Commission and Marketing Authorisation Holders. No direct obligations are placed on the other actors by EU legislation. Overall, the current EU pharmacovigilance system is organised with functions, responsibilities and accountability shared between the Member State competent authorities, the EMEA and European Commission. The EMEA has responsibility for co-ordinating the pharmacovigilance activities of the Member States. The stakeholders involved in / affected by pharmacovigilance are provided in Table 1.

Table 1 Overview of main stakeholders involved / affected.

Stakeholder group	Main role in pharmacovigilance
Citizens	
Patients / consumers	The users of medicines
Relatives	Advise to and care of patients
Healthcare professionals working with medicines	
Physicians	Advise + prescribe meds + report ADRs
Pharmacists	Advise + dispense meds + report ADRs
Nurses	Advise + administer meds + report ADRs
Academia	Conduct studies on medicine safety
Member States	
National Health Services	Delivery of healthcare
Government payers / social insurance schemes	Payment: healthcare incl. medicines
Medicines authorities / agencies	
European Medicines Agency (EMEA)	Coordination of pharmacovigilance
EEA National agencies (competent authorities)	Collect, assess and act on data
EEA regional monitoring centres	Collect data for national agencies
International regulatory authorities	Collaboration with EU on PhV
Industry	
Marketing Authorisation Holders[8]	Operate a pharmacovigilance system including risk management and studies, report ADRs, PSURs.

[8] MAHs are often broken down by the type of products they market, as follows: innovative medicines, generic medicines, orphan (medicines for rare diseases), biotechnology medicines, plasma-derived

The exact division of responsibilities changes depending on how a particular medicine is authorised. If a medicine has been authorised through the national authorisation mechanisms, most (but not all) of the functions, responsibilities and accountability for pharmacovigilance rest with the Member States. In contrast, for centrally authorised medicines, that is, those authorised through the central Community authorisation procedure, more of the functions, responsibilities and accountability for pharmacovigilance belong to the EMEA and European Commission.

To put the effects of weaknesses in the EU pharmacovigilance system into context the public health burden of ADRs should be noted. Best estimates from the medical and scientific literature suggest that:

- 0.12%-0.22% of hospital admissions result in death due to an ADR corresponding to 100,800- 197,000 deaths annually in the EU.
- 3-10 % of hospital admissions are caused by ADRs corresponding to 2.5-8.4 millions annually in the EU.
- 2.1–6.5% of hospitalised patients suffer an ADR, corresponding to 1.8-5.5 million annually in the EU.
- ADR-related costs other than those caused by hospitalization are estimated at €63.2 billion annually in the EU.
- € 79 billion represents a reasonable estimate of the total societal cost of ADRs occurring in the EU.

What is the problem?

The first EU legislation on pharmacovigilance was adopted in the 1960s. Since then the rules have gradually become more complex. The pharmaceutical legislation was last updated in 2004 (the so-called '2001 – Review'). The 2001-Review did not include a systematic review of the EU pharmacovigilance rules and did not assess their effectiveness. Certain changes to the pharmacovigilance rules were included based on codifying case law from the European Court and based on issues raised by the European Parliament. Some of the pharmacovigilance changes introduced as a result of the 2001-Review significantly increased administrative burden without necessarily improving public health protection. Perhaps the best example of this is the introduction of the requirement for submission of a detailed description of the company pharmacovigilance system at the time of authorisation which then needs to be maintained up to date with regulatory scrutiny (and payment of 'variation fees' for each and every minor improvement to the company system). Other novelties of the 2001-Review do show promise in improving the protection of public health

---

medicines, radiological products, vaccines, non-prescription (OTC) medicines, herbal products, homeopathic products.

such as the introduction of risk management systems, however, the legal drafting was such that these are difficult to enforce, particularly for products already on the market.

Based on the independent study, a public consultation, and analysis by Commission services, there is concrete evidence that the current EU system of pharmacovigilance is heavily bureaucratic, with strong reliance on paper based reporting of suspected adverse reactions by health professionals. Such data, although critically important, need to be supplemented by more proactive collection of higher quality data relevant to product safety. It has been suggested that more proactive and robust safety monitoring could have led to early detection of the safety problems that lead to the withdrawals of Vioxx® and Celebrex®, two widely used pain killers discovered to cause cardiac (heart) failure as an adverse reaction, reportedly linked to thousands of deaths (Case study 1 below).

Case Study 1: Vioxx® withdrawal

Rofecoxib is a nonsteroidal anti-inflammatory drug that was used to treat osteoarthritis, acute pain conditions, and dysmenorrhoe. Rofecoxib was approved as a safe and effective medicine in 1999 and was subsequently marketed under the brand name Vioxx.

Rofecoxib gained widespread acceptance among physicians treating patients with arthritis and other conditions causing chronic or acute pain. Worldwide, over 80 million people were prescribed rofecoxib at some time.

On September 30, 2004, the marketing authorisation holder voluntarily withdrew rofecoxib from the market because of concerns about an increased risk of heart attack and stroke associated with long-term, high-dosage use. Rofecoxib was one of the most widely used drugs ever to be withdrawn from the market. In the year before withdrawal it had sales revenue of €2.3 billion.

As of March 2006, there had been over 10,000 legal cases and 190 class actions filed against the company over adverse cardiovascular events associated with rofecoxib and the adequacy of the product warnings. The company has reserved $970 million to pay for its Vioxx-related legal expenses through 2007, and has set aside $4.85 billion for legal claims from US citizens. Patients who claim to have suffered as a result of taking Vioxx in countries outside the US are campaigning for this to be extended.

The EU legal framework for pharmacovigilance is complex and unclear with reporting and assessment being duplicative. Furthermore there is a lack of clear roles and responsibilities.

Disharmony regarding pharmacovigilance requirements increases regulatory burden on the industry and divergent action is often taken by the Member States regarding the same safety issues which is an impediment to the single market in pharmaceuticals. There are hundreds of examples over recent years of safety issues being discussed at the EMEA Pharmacovigilance Working Party (i.e. at community level) where the conclusions reached are never made public. Furthermore the conclusions are implemented by some Member States and not by others or are implemented to different degrees in different Member States or at different times by different Member States. Such divergent action, frequently relating to warnings in product information leads to divergent warnings for patients crossing borders, high costs for companies in terms of packaging and product information for different Member State markets, a lack of clear reference safety information when authorising generic products and, overall, interference in the free movement of goods. This disharmony in decision-making and regulatory action is exacerbated by the lack of transparency relating to the EMEA Pharmacovigilance Working Party.

A rationalisation and strengthening of pharmacovigilance is particularly pressing now with the introduction of innovative products, some utilising innovative technologies. Furthermore, with globalisation of the pharmaceutical market, products often enter different global markets simultaneously with exposure of a large numbers of patients occurring in a short period of time. European society is changing and the expectations of Community citizens are also shifting. There is a need to ensure that our pharmacovigilance systems are robust but also transparent and we must consider the appropriate level of involvement in the system of different stakeholders, including healthcare professionals and patients**.**

There is a clear link between robustness of pharmacovigilance and innovation. As well as investor confidence in funding pharmaceutical R&D being linked to pharmacovigilance, regulatory authority decision-making when authorising products is directly linked to the robustness of post-authorisation safety monitoring (pharmacovigilance): if regulators are confident in the pharmacovigilance system and for example, post-authorisation safety studies will be conducted, then they will be more likely to allow a product into market and this is of crucial benefit to patients with unmet medical needs. Therefore, if there are weaknesses in the EU pharmacovigilance system this will decrease confidence and decrease the likelihood of innovative products being developed authorised and thus being available to meet the unmet needs of patients.

Because of the enormous societal burden from the public health impact of ADRs, weaknesses in the EU pharmacovigilance system have a major negative impact. The significant weaknesses of the current EU system of pharmacovigilance that have been identified can be grouped as follows:

- A lack of clear roles and responsibilities for the key responsible parties and a lack of clear obligations against which they perform their roles (resulting in poor compliance);

- Slow EU decision-making on drug safety issues particularly for nationally authorised products and frequent disharmony in action taken by the Member States;

- Low levels of transparency relating to pharmacovigilance and relatively limited EU coordination of communication about the safety of medicines, plus complex product information with poor penetration of key warnings;

- Cumbersome oversight of companies' pharmacovigilance systems by the authorities;

- A lack of proactive and proportionate monitoring including a lack of risk management and structured data collection in the form of post authorisation safety studies and duplicative reporting rules for the industry and authorities relating to both 15-day, literature and periodic (PSUR) reporting of ADRs;

- Lack of inclusiveness of stakeholders including a lack of direct patient reporting of ADRs and their virtual absence from decision-making.

These problems are directly linked to the objectives and this link is presented schematically in Section 3.

2.1.3. A lack of clear roles and responsibilities

Currently the roles, responsibilities and standards for pharmacovigilance are defined vaguely, leading to poor compliance:

- The respective roles of the Member States and the European Medicines Agency (EMEA) are over-lapping with the current lack of clarity.
- The elements making up a national pharmacovigilance system are not clearly listed with no standards placed on the Member States (which are obliged to establish them).
- The breadth and depth of guidelines and their interface with legislation is not well defined.
- As the standards for companies' pharmacovigilance systems are not precise in the legislation there is a lack of clearly defined standards for their inspection by the authorities.
- Although some tasks are defined in the legislation for the company's "qualified person for pharmacovigilance" these are far from comprehensive.
- The legal requirement on industry to notify the competent authorities on urgent drug safety issues is currently ambiguous with respect to timing e.g. regulators were notified of the company withdrawal of Vioxx® on the same day as the public announcement.
- Some Member States could continue to fail to supply quality data to the EU data-processing network and database (Eudravigilance) system due to unclear responsibilities for delivery.

2.1.4. Slow EU decision-making on drug safety issues

Decision-making (referrals) at European level depends on how the medicinal product was authorised (centrally by the Commission, through mutual recognition or purely nationally). Particularly for non-centrally authorised products decision-making is slow, and lacking transparency.

Due to unclear and overlapping legal provisions on referrals, when a Member State considers an important safety issue relating to a nationally authorised product, the Community referral procedures are rarely used. Instead the existing 'Pharmacovigilance Working Party' of the EMEA informally discusses important safety issues, but its conclusions are rarely implemented and certainly not implemented comprehensively and consistently across all Member States (as they are not legally binding on the Member States or companies). This may lead to delays in debating new or changing safety issues and delay in reduction of the risks to patient. Divergent safety action by the Member States represent a weakness of public health protection, create obstacles for the single market and are costly for the industry.

A lack of legal certainty, the lack of proactive safety monitoring including a lack of safety studies, combined with slow and cumbersome EU action in response to drug safety alerts

puts patient safety at risk. Safety withdrawals of blockbuster products such as of rofecoxib in 2003 and cerivastatin (Lipobay® – Bayer) in 2001 were due to fatal adverse drug reactions where the conditions being treated were not life threatening and alternative treatments were available. If the problems could have been detected earlier, with earlier decisions and action taken, lives could have been saved and suffering from adverse drug reactions to medicines could have been prevented.

2.1.5. Low levels of transparency and uncoordinated communication

Lack of transparency

Rules for both transparency and communications are partly in law and partly in guidelines and are not always coherent. Communications about drug safety are frequently not coordinated at EU level leading to contradictory messages when patients access media from different Member States. Civil society is increasingly asking for more openness in the operation of Regulatory Authorities. Although since its establishment, the EMEA has taken various actions to increase its transparency, new initiatives are needed to meet the increasing demands of patients, healthcare professionals and the general public. Such transparency initiatives should include more proactive disclosure of documents, access to pharmacovigilance data, timely and more efficient handling of a steadily increasing number of requests for information and requests for access to documents, development and implementation of better communication tools, etc.

Product information

The current organisation of Summary of Product Characteristics and Patient Information Leaflet (documents being approved by regulatory authorities as a part of marketing authorisation decision) makes it difficult for patients, but also for prescribers, to identify the most important safety warnings: this results in key safety measures/warnings being missed.

2.1.6. Cumbersome oversight of companies' pharmacovigilance systems

Companies are also required to submit a detailed description of their pharmacovigilance system (DDPS) as part of the marketing authorisation application, which has to be kept up to date through variations to the marketing authorisation. The frequency of changes to company DDPS is quite high, since these are, for instance, required also for relatively minor changes in the company global organisation outside the EU.

This requirement represents a major administrative burden at present for industry and regulators because any change to a company system has to be implemented through a variation to the marketing authorisation (for each product and each national authority). If the current law is complied with a minor change in a company's pharmacovigilance system could necessitate hundreds of variations to marketing authorisations in the Member States.

2.1.7. A lack of proactive and proportionate monitoring and duplicative reporting rules

Risk management planning

Risk Management Plans, which are required for some products at the time of authorisation in order to ensure prospective safety evaluation of products, are frequently not agreed or when agreed the industry may not fully comply with them (frequently post-authorisation

safety studies are not conducted or completed). Under current provisions ensuring compliance by the company with measures in a risk management system (how risks will be monitored and risks to patients reduced e.g. through post-authorisation safety studies) would remain problematic as the legal requirement is to describe the measures not to conduct them. In addition, the legal basis for requesting risk management plans for authorised products is currently unclear and different authorities are using different legal provisions.

Low quality post-authorisation safety studies

Post-authorisation safety studies form an essential part of risk minimisation activities and already involve substantial industry resources. Nevertheless conducted studies are often of poor quality and frequently conducted for promotional rather than safety reasons. In the current EU legislation there are no guiding principles and there is no oversight of non-interventional safety studies. There is an EU guideline but it does not ensure harmonised practice. Therefore there are divergent national measures (including legislation in some Member States) that interfere with the single market and make the conduct of these studies difficult.

Duplicative adverse drug reaction case reporting

Companies are obliged to record and report individual reports of serious suspected adverse drug reactions (ADR) to the competent authorities within 15 days (expedited reporting). The current complex rules for expedited ADR reporting result in the same reports being sent in different formats from multiple senders to multiple receivers creating major bureaucratic burden. This also leads to duplicate reports being in the databases, making data evaluations much more difficult. There are currently legal requirements on national competent authorities receiving reports of suspected ADRs directly from healthcare professionals to pass these on to the MAHs, the EMEA and the other national competent authorities, and this further exacerbates the merry-go-round of ADR reports passing between multiple senders and receivers.

Different implementation of the current legal provisions by Member States has led to diverse reporting requirements, which creates heavy costs on industry and regulators and clearly interferes with the functioning of the single market for medicinal products. As a consequence, both industry and regulator resources are diverted away from public health protection to meeting duplicative administrative requirements. There is major scope for simplification by eradicating unnecessary duplication of reporting and by maximising the use of modern information technology.

Submission of case reports of adverse reactions from the worldwide scientific literature to the authorities is currently an obligation on all companies leading to the same literature case report being submitted to multiple authorities by sometimes hundreds of companies (for generic medicinal products).

Lacking framework for reporting of medication errors

Medication errors likely represent the most common single preventable cause of adverse events. The Council of Europe Medication Safety Report recommends Member States to establish medication errors reporting systems as a component of or to complement patient safety incident reporting systems for incidents involving medicines. However, there is no EU framework established to exchange information between national competent authorities

for medicinal products and authorities for patient safety within that Member States. Current EU medicines legislation is unclear on companies reporting of medication errors to the competent authorities for medicines so that not all relevant safety data are available to assess the safety of medicines.

Duplicative periodic safety update reports

Periodic safety update reports (PSURs) are the periodic reports that the MAHs have to submit to the concerned agencies containing the individual case safety reports the MAH has received in the last period, as well as any other safety-relevant information.

Currently, major resource is expended by industry and regulators on PSUR production and assessment with questionable public health benefit. There is lack of correlation between the reporting requirements and the risks posed by the product. There is major duplication of reporting to different national authorities and duplication of assessment. Example: hundreds of companies have authorisations for paracetamol products and produce hundreds of PSURs which are submitted to the 30 EEA Member States who then assess them in an uncoordinated way.

2.1.8. Lack of inclusiveness of stakeholders

The current EU Pharmacovigilance system does not engage the spectrum of stakeholders affected by the safety of medicines as listed in section 2.3.1.

The need for patients to be empowered by allowing them to report the side effects they experience to their medicines was a key outcome of the 2006 public consultation. Currently patients in some Member States but not in others are allowed to report directly the side effects they experience to their medicines. This limits the data available on the safety of medicines and leads to citizens considering themselves passive parties.

The current EU committees responsible for pharmacovigilance do not systematically involve / interface with healthcare professionals and patients and this denies these key-stakeholders a voice in decision-making on safety issues and means that decisions are may be taken without all the relevant experience and information being made available.

This lack of inclusiveness of stakeholders in the processes of pharmacovigilance, coupled with the lack of transparency have an additive affect in reducing the trust of patients in the regulation of medicines and more generally in the pharmaceutical industry. There is evidence for this lack of trust including the results of public consultation, a report of a national parliamentary committee[9] and multiple papers in the medical literature[10].

Does the EU have the right to act? Treaty legal basis and subsidiarity

---

[9] Report *Ordered by The House of Commons*: The Influence of the Pharmaceutical Industry. March 2005
http://www.parliament.the-stationery-office.co.uk/pa/cm200405/cmselect/cmhealth/42/42.pdf

[10] BMJ 2007;334:209 (27 January),
http://www.bmj.com/cgi/content/full/334/7586/209?maxtoshow=&HITS=10&hits=10&RESULTFORMAT=&fulltext=seroxat&searchid=1&FIRSTINDEX=0&sortspec=date&resourcetype=HWCIT

The objectives of the proposal are consistent with the overall objective of the Community pharmaceutical legislation of removing disparities between national provisions in order to ensure the proper functioning of the internal market for medicinal products, while at the same time safeguarding a high level of protection of public, human and animal health.

Following the entry into force of the Treaty of Amsterdam, all the legislative provisions adopted by the European Parliament and the Council, except for directives adopted on the basis of the executive powers conferred on the Commission and seeking to align the provisions on medicinal products, are adopted on the basis of Article 95 of the Treaty as a legal basis for achieving the objectives set out in Article 14 of the Treaty, which include the free movement of goods and hence of medicinal products for human use. This is because the differences between national laws, regulations and administrative provisions on medicinal products result in obstacles to intra-Community trade which directly affect the operation of the internal market.

The proposal also respects Article 152(1) of the Treaty establishing the European Community, which lays down that a high level of human health protection shall be ensured in the definition and implementation of all Community policies and activities. Common EU approach allows sharing of best practices and aggregation of nationally collected safety data enhances sensitivity of safety risk detection. Given that this will make it possible to take advantage of the widest possible market-surveillance and avoid the dispersion of limited resources, the Community may adopt measures in accordance with the principle of subsidiarity as set out in Article 5 of the Treaty.

Considering existing EU legislation, functioning of the single market and the increasing share of centrally authorised medicinal products, action of Member States alone would not be sufficient to bring full harmonisation of Pharmacovigilance rules between Member States and the objectives of this legal proposal can only be fully achieved at the Community level. Legislative action by the Community is therefore justified in order to prevent or remove such obstacles.

3. OBJECTIVES

General policy objectives

The overall objectives of the Community pharmaceutical legislation are:

- to ensure proper functioning of the internal market for medicinal products
- to better protect health of the EU citizens

Specific objective

The specific objective of the Commission's legislative proposals is to improve the health of EU citizens by strengthening and rationalising pharmacovigilance.

Operational objectives

The specific objective can be achieved by:

Providing for clear roles and responsibilities for the key responsible parties and clear obligations against which they perform their roles;

Rationalising EU decision-making on drug safety issues in order to deliver measures that are equally and fully implemented for all relevant products and across the community with a view of preventing unnecessary patient exposure to risks;

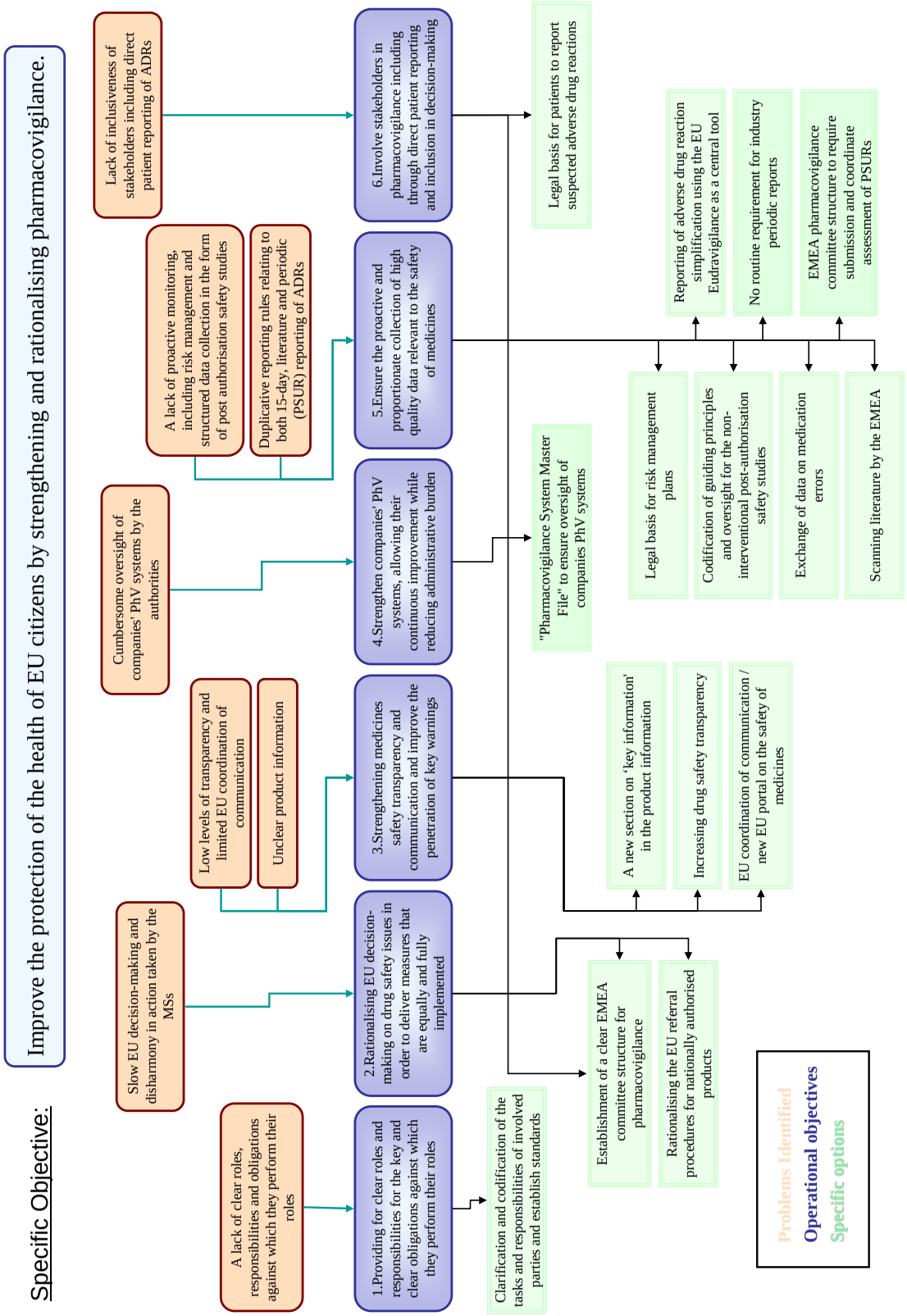
Strengthening medicines safety transparency and communication to increase the understanding and trust of patients and health professionals in the safety of medicines and improve the penetration of key warnings;

Strengthen companies' pharmacovigilance systems, allowing companies to improve their systems constantly while reducing administrative burden;

Ensure the proactive and proportionate collection of high quality data relevant to the safety of medicines through risk management and structured data collection in the form of post authorisation safety studies, together with rationalised single case and periodic reporting of suspected adverse reactions;

Involve stakeholders in pharmacovigilance including through direct patient reporting of suspected adverse reactions and inclusion of patients and heath-care professionals in decision-making.

Schema 1 The link between the identified problems, the operation objectives and the specific policy options



4. POLICY OPTIONS

Basic options

In the course of the discussions with experts and stakeholders, four basic policy-options have been developed no policy change, deregulation, self regulation and amendments to the existing European Community legislation.

4.1.1. No Policy-Change

One option could be to leave the current situation unchanged. This would mean that the existing Directive 2001/83/EC and Regulation (EC) No.726/2004 would not be revised and that the current standard of community legislation and national implementation of legislation would continue.

Some problems and trends of concern are already being addressed through improved implementation and better enforcement of the existing legislation including:

- Working with the Commission's Directorate General for Research on funding of studies into the safety of medicines, as well as, studies into the methodologies used to conduct pharmacovigilance.

- Working with the Member States to identify and resolve implementation issues, including and administrative practices that interfere with the single market.

- Working with the EMEA to strengthen its coordinating role including supporting full compliance and maximum utilisation of the EU pharmacovigilance database 'Eudravigilance'.

- Revising pharmacovigilance guidelines (Eudralex Volume 9A).

This improved implementation and enforcement work will improve pharmacovigilance and EU public health protection to a degree. However, the impact overall will be limited and the step change improvement in public health protection can only be realised with a change to EU legislation. Specifically, the majority of the objectives put forward in section 3 of this report can only be realised through a change of EU legislation because the subject matter or processes involved are governed by existing EU legislation. Furthermore, while many Member States have shown themselves willing to work collaboratively to enhance the operation of the EU pharmacovigilance system, many of the divergent National requirements placed on industry and the difficulties in collecting and managing high quality data relevant to the safety of medicines at EU level have their roots in the current ambiguous provisions in EU legislation.

4.1.2. Deregulation

In theory, the existing provisions in the Directive and Regulation could be repelled and the regulatory competence for nationally registered products fully transferred to the Member States, with the European Community level remaining to provide only recommendations and playing an active part in exchanging information on good practices and alternative methods. This option of deregulation was not pursued further because all Member States have existing national legislation that implements the existing EU Directive. Also,

deregulation would naturally lead to an even more uneven playing field and more acute problems with the Single Market. Furthermore, the impact of deregulation would fail to address the calls from experts, stakeholders, Member States and policy makers who have reached a broad consensus during the last few years on the fact that a revision of the current legislation is necessary. Finally, deregulation is clearly not advisable in view of the international commitments (ICH) of the European Community and procedures and mechanisms within EMEA. The question therefore is not whether the EC should regulate but how it should regulate.

4.1.3. Self-Regulation

It should be acknowledged that the current EU regulatory framework places important obligations on the pharmaceutical industry. Notably the legislation requires the "Marketing Authorisation Holder" to monitor the safety of its products, operate a pharmacovigilance system and notify the authorities reports of suspected ADRs. Transferring the entire responsibility for product safety to the companies marketing medicinal products is also a theoretical possibility. However, the development, manufacture, authorisation, labelling and surveillance of medicinal products is highly regulated and has been so, even at an EU level, for 40-years. This high level of regulation reflects the highly specialised knowledge needed to use medicines safety and effectively and because of the extreme dangers posed by medicines when used incorrectly. Public health disasters, such as the thalidomide tragedy of the 1950s and 1960s which led to the introduction of strict medicines regulation, remind us

Case Study 2: Thalidomide – the active ingredient of a hypnotic agent which was sold was sold from 1957 to 1961 in almost 50 countries under at least 40 brand names - triggered a global tragedy. As there were no clear legislative requirements for the development, production and marketing of medicinal products in mid-1950s, it was possible to introduce the hypnotic agent manufactured on the basis of thalidomide on the market in 1957 without any governmental review of the documentation.

Thalidomide was commonly sold and prescribed to pregnant women, as an antiemetic to combat morning sickness and as an aid to help them sleep. It was in the autumn of 1961 when the first surveys suggested suspicion that thalidomide products might possess a teratogenic (defect-causing) effect and the company withdrew its thalidomide products from the market. From 1956 to 1962, approximately **10,000 children** were born with severe malformities, because their mothers had taken thalidomide during pregnancy.

This experience, which shook public health authorities and the general public, made it clear that to safeguard public health; no medicinal product must ever again be marketed without prior authorisation. Much of the impetus behind the first European Community pharmaceutical Directive 65/65/EEC stemmed from determination to prevent a recurrence of the thalidomide disaster.

Other countries enacted similar legislation, and thalidomide was not prescribed or sold for decades. Researchers, however, continued to work with the drug. Subsequent research in 1990's has shown that it is effective in multiple myeloma, and it has been recently authorised by the EMEA for the treatment of this rare cancer of the bone marrow.

The CHMP has approved a risk management plan that includes a number of actions intended to prevent pregnancies in women being treated with thalidomide and exposure of unborn children to the medicine. For example, all women of child-bearing potential who are treated with "Thalidomide Pharmion" must undergo pregnancy tests before, during and after treatment, in addition to using selected and effective contraception. Subject to the granting of a marketing authorisation by the European Commission, thalidomide will only be available by prescription only, and treatment will be initiated and monitored by a doctor who has experience in the treatment of multiple myeloma. A clear warning will be printed on the boxes containing the medicine, indicating that "Thalidomide Pharmion" causes birth defects and foetal death.

of the consequences of uncontrolled or poorly controlled use of medicines.

While some sections of the industry might responsibly try to maintain the safety of their products, issues of patient confidentiality, lack of trust of patients in the industry and absence of data collection mechanisms would inevitably mean that public health would be put in at extreme risk. Deregulation or self regulations are not being requested by any impacted stakeholders, and notably not the industry. Our stakeholders are calling for better health promotion and protection through strengthened and rationalised pharmacovigilance. Finally, even within the current regulatory framework there is evidence that compliance of the industry with pharmacovigilance rules is not complete. Therefore a move to self regulation without oversight would be likely to lead to substandard or even absent pharmacovigilance by some companies and this would put public health at greater risk.

4.1.4. Amendments to the existing European Community legislation

Another option could be to reinforce the European Community level regulation by revising the existing Directive and Regulation. This would mean that in specific areas, where evidence shows that a Community wide harmonisation could considerably contribute to the enhancement of public health protection and to a reduction of existing obstacles to the functioning of the internal market a revised Directive and Regulation would set clearer and more harmonized standards. The current system for the regulation of medicines is a Europe-wide system. Therefore, an efficient and effective way to strengthen public health protection through pharmacovigilance is via the existing Community system of pharmaceutical legislation. Given the Community nature of the existing pharmaceutical legislation, the scope for unilateral action by individual Member States is limited. Amendments to the existing EU legislative framework allow to provide as many wins and winners as possible. It allows options that build on and link existing Community and Member State, structures, institutions, processes and mechanisms. Strengthening pharmacovigilance through amendment of the existing EU legislation thereby also respects the division of competencies between the Community and the Member States and ensures that the measures are efficient, effective and consistent.

It should be emphasised that the current EU regulatory framework for pharmacovigilance comprises high level provisions in a directive and regulation and then very detailed non-binding guidelines (notably Volume 9A of Eudralex). One of the key issues that has been detected during the independent study and during public consultation is that necessary principles, responsibilities and obligations are absent in EU legislation and the detailed non-binding guidance often tries to fill the void. This has the effect of guidance placing de-facto obligations on industry and regulators. Not surprisingly compliance with these guideline obligations is patchy and there is frequently no basis for enforcement action because of the absence of clear provisions in EU legislation. On this basis it appears appropriate to strengthen the EU legislation rather than add to the already extensive but difficult to enforce guidelines. Where guidance is proposed, its legal basis and scope should be clear and the proposals have been developed with this aim.

Specific policy options

The first round of public consultation conducted in 2006 was an exercise in listening to stakeholders on how the EU system for pharmacovigilance could be strengthened and rationalised. This first consultation made no specific proposals for change. The analysis of

the response to the first consultation, including detailed dialogue with experts and the results of the independent study clearly identified the problems outlined in Section 2 and also resulted in numerous concrete suggestions for how the system could be improved. These suggestions are detailed in Annex 1. The Commission services analysed these suggestions in terms of whether they fell within the scope of the current project, their legality, practically and cost and discussed the options to strengthen the system with the Commission inter-service group and with stakeholders including industry and regulatory experts.

By the autumn of 2007 consensus within the Commission inter-service group and with stakeholder experts was emerging on fifteen specific policy options. These therefore formed the basis of the second public consultation launched in December 2007. There was broad support from the second public consultation for all fifteen specific options, however, detailed comments on impact including practicality lead to important amendments to some of them. While this section describes the fifteen specific policy options in a high level way, the evolution of those options that have changed is presented in Section 5.2 and is further elaborated in Annex 3 where certain alternative specific policy options are also included.

I. Clear roles, responsibilities and obligations

In view of the large differences in current practices, the overlapping and ambiguous responsibilities for pharmacovigilance and the dispersed rules partly in law and partly in guidance, clarification of responsibilities and codification of standards for stakeholders should ensure that the parties know what is expected of them and this will support inspection and audit (and thus quality management).

Option 1: Clarify and codify the tasks and responsibilities of involved parties in the legislation: For the Member State competent authorities, EMEA, Commission and Marketing Authorisation holders, clarify and codify the tasks and responsibilities in legislation. To support inspections and quality management, establish the concept and scope of Good Vigilance Practices (GVP) in co-decision texts and create the legal basis for the Commission to adopt a guideline on ‘GVP’ via comitology.

II. Rationalise EU decision-making

Fast EU decision-making on safety issues by rationalising the existing EU referral procedures and reinforcing the EU committee structure should ensure that important safety issues are rapidly and robustly dealt with in one coordinated, fast and effective EU procedure rather than disparate national reviews, studies and actions.

Option 1: To establish an EU committee structure on pharmacovigilance: Within the EMEA, establish a committee structure (to replace the existing Pharmacovigilance Working Party) with clear responsibility for coordinating pharmacovigilance and for making recommendations on the safety of medicines.

Option 2: Rationalise the EU referral procedures for nationally authorised products: Establishment of an automatic pharmacovigilance referral procedure with non-discretional referral triggers placed on the Member States to ensure that for important safety issues safety action is taken in all Member States to protect the health of European patients.

III. Transparency, Communication and penetration of key warnings

Strengthened medicines safety transparency and communication should increase the understanding and trust of patients and health professionals in the safety of medicines and the regulatory system. Clear, EU coordinated messages about specific safety risk issues will improve the safe use of medicines.

Option 1: Increase drug safety transparency: Codify existing legal and guideline provisions on transparency and communication. Transparency initiatives should also include more proactive disclosure of documents (e.g. agendas and minutes of meetings), access to EudraVigilance data, timely and more efficient handling of a steadily increasing number of requests for information and requests for access to documents, as well as, development and implementation of better communication tools.

Option 2: EU coordination of communication about major safety issues and establishment of the EU portal on the safety of medicines: **The principles of communication (including roles and timing) about major new or changing safety issues should be laid down in law. For major safety issues including safety issues affecting drug substances authorised in more than one Member State the legal basis should be clarified for the EMEA to coordinate (but not replace) the communications of the Member States. Furthermore, the EMEA should set-up and maintain an EU portal on the safety of medicines. The EU site would be the main platform for all announcements related to medicines safety dealt with at the EU level and would include links to websites of the Member State competent authorities. MAHs would be obliged to monitor regularly the safety portal and update their product information in line with safety recommendations.**

Option 3: Introduction of a new ‘key safety information' section in Product Information: New sections on ‘key safety information' should be inserted in the Summary of Product Characteristics and Patient Information Leaflet, key sources of information for health care professionals and patients respectively, thereby allowing them to rapidly identify critical messages about the medicinal product.

IV. Company pharmacovigilance system

Currently legislation requires a ‘detailed description of the pharmacovigilance system’ to be submitted to authorities and kept up to date for each individual marketing authorisation.

Option 1: Introduction of "Pharmacovigilance System Master File": This would simplify the existing requirement for a ‘detailed description of the pharmacovigilance system’ to be submitted and kept up to date. At marketing authorisation only key elements of the pharmacovigilance system should be submitted as a part of the dossier. This simplification with a requirement for companies to maintain a detailed file on site on their Pharmacovigilance System ("Pharmacovigilance System Master File") and this will be submitted on request by the authorities or can be viewed during inspections.

V. Ensure proactive and proportionate collection of high quality data on the safety of medicines

Pharmacovigilance should be planned proactively and should be risk based. Decisions about the safety of medicines should be based on the highest quality data possible. Duplicate reporting rules should be simplified and use should be made of modern information technology and work-sharing.

Risk management planning and non-interventional safety studies

Option 1: Clear legal basis for risk management plans for new and authorised products with safety concerns, including post-authorisation safety studies: Rationalising of risk management planning should ensure that safety evaluation of products is prospective (i.e. based on risk management planning) and that high-quality, non-promotional EU safety studies are done (i.e. there is compliance) when justified by safety concerns. Clarification of the legal requirement to submit a risk management plan at the time of the marketing authorisation application and inclusion of risk management measures in the marketing authorisation, thereby making them legally binding and ensuring that marketing authorisation holders conduct the measures specified and provide updates to the competent authority and the EMEA as specified in the risk management plan. Requirement for risk management plans, including post-authorisation safety studies when there is a public health concern with an existing authorised product so that safety issues are rapidly detected, and effectively dealt with, based on robust data.

Option 2: Codification of guiding principles and oversight for the conduct of non-interventional post-authorisation safety studies: **Codification of guiding principles for the conduct of non-interventional post-authorisation safety studies, i.e. safety studies of marketed products that are not clinical trials. Light oversight by NCAs or by the EU new pharmacovigilance committee structure, if conduct to be in more than one Member State, of such studies to ensure that they have health rather than promotional objectives.**

Adverse drug reaction case reports

Reporting of suspected adverse drug reaction (ADRs) this is currently very complex, duplicative and burdensome. The options should simplify and make proportional reporting of single adverse drug reaction (ADR) case reports, and ensure that overdoses and medication errors are reported to the relevant authorities with a clear legal basis.

Option 3: Simplification of ADR reporting using the EU Eudravigilance database as a central tool: All non-EU individual safety case reports and EU domestic reports to be reported by companies to the EU Eudravigilance database only.

Option 4: Scanning of the scientific literature by the EMEA: The EMEA to take on a new task, clearly defined in scope, for scanning of the scientific literature and entering case reports of adverse effects of medicines onto Eudravigilance, rather than the duplication currently conducted by the industry.

Option 5: Medication errors that result in an adverse reaction should be reported to the competent authorities for medicines: The definition of adverse drug reaction should be clarified as would the ADR reporting rules to make clear that companies report medication errors that result in an adverse reaction to the competent authorities for medicines and ensure that all the relevant Member State authorities share data (including between the authorities for medicines and any authorities for patient safety).

Periodic safety update reports

Regarding periodic safety update reporting, current paper based reporting leads to the same periodic report being submitted to numerous medicines agencies and duplicative assessment. The proposed options would simplify and make proportional to the knowledge

about the safety/risk of the product, periodic safety update report (PSUR) submission by industry and ensure faster product safety assessment and faster updating of product information.

Option 6: Removal of the current routine requirement for PSURs for low risk, old and established products: Remove the routine requirements for uncoordinated submission of PSURs for older products (instead have ad-hoc requests for PSURs of such products) and link PSURs to risk management planning and therefore the knowledge about the safety of the product.

Option 7: Provide the legal basis for the EU pharmacovigilance committee structure to coordinate assessment of PSURs and make recommendations for product labelling: **Member States, within the current framework, are piloting PSUR assessment work-sharing on a voluntary basis. This option would provide a legal basis for this worksharing with a clear coordinating role for the new EU pharmacovigilance committee structure**. **Furthermore, its conclusions regarding warnings for product information would be posted on the EMEA website and the MAH would be obliged to take account.**

VI Involve stakeholders in pharmacovigilance

Option 1: Clear legal basis for patients to report suspected adverse drug reactions: Harmonise the legal basis for patients to report suspected adverse drug reactions. For new innovative medicines, information on how to report adverse reaction to be included in the patient information leaflet and for all other drugs reporting to be directly to the national authority, via web-sites.

5. ANALYSIS OF IMPACTS

The impacts have been analysed with benefits assessed according to the key problem dimensions (public health/societal, economic, environmental issues) and costs were assessed according to whether they occur for marketing authorisation holder (innovative/biotech/generic/OTC/SME), for regulatory authorities (EU/national), patients, health professionals or other key stakeholders.

The basic benefit and cost model normally assesses the impacts against existing provisions, i.e. “no policy change”. The relative strength of an impact is qualified as "slight", "moderate" and "high" (+, ++ or +++) according to the feedback from stakeholders or available literature references. It is clear that these qualifications express subjective views; however, many of the impacts are very difficult or impossible to measure in absolute figures. Absolute figures are provided where available.

The following assumptions and extrapolations were made in line with official European statistics:

- Population of the EU-27: 493,119,161 (2007 estimate).
- Turnover of the EU pharmaceutical market: €140.7 billion (Eurostat, 2005).
- Number of enterprises producing pharmaceutical preparations: 3700 (Eurostat, 2005).
- Number of ADRs received by NCAs in the EEA per year: 100,036 (2004).
- Number of PSURs received by NCAs in the EEA per year: 17,630 (2004).
- Number of PhV personnel in the EEA NCAs: 317 (for EEA in 2004).

- Average hourly wage for researchers and public officials in the EU-27: 35 € + 40% overheads.

It will be indicated in Section 5.2 if an option has been discarded or revised in the light of the impact assessment or comments received in the most recent public consultation and the evolution of specific policy options is further elaborated in Annex 3.

5.1. Methodology of impact quantification

This section outlines key principles of quantification of impacts in three key areas identified, which are described in detail at Annex 2:

- Public health burden of adverse drug reactions
- Industry resources deployed in pharmacovigilance
- Regulatory resources deployed in pharmacovigilance

5.1.1. Public health burden of Adverse Drug Reactions (ADRs)

Incidence of ADRs

There are several sources that can give information on ADRs and their frequency. These include clinical trials, case reports and epidemiological studies. The incidence of all ADRs occurring in society is difficult to estimate. However, the incidence in hospitalised patients and the number of ADRs leading to hospital admissions have been investigated in several systematic studies published in the medical literature.

Cost Classification

ADRs are a common cause of morbidity and mortality with a considerable negative impact, not only on the health of the population, but also on health care costs. ADRs represent a burden that diminishes the true value of medicines. The negative economic impacts of ADRs to any society could be further classified as:

Direct costs: refer to costs falling on the health sector in relation to prevention, diagnosis and treatment of disease, e.g. ambulances, inpatient care, outpatient care, rehabilitation, community health and medical services, and pharmaceuticals.

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').

Intangible costs: capture the psychological dimensions of the illness to the individual (and their family), including pain, bereavement, anxiety and suffering

The estimation of indirect and intangible costs is complicated because necessary information is often difficult to measure and therefore almost no original research on indirect and intangible costs of ADRs could be found.

Cost Quantification

Adverse effects have an impact both on health and on resource utilisation. The measurement of the costs of those ADRs that caused a death or lead to hospitalization are the most straightforward. 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 were 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 (see Annex 2 for an in-depth analysis).

Measured costs fall into three categories:

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

Burden of adverse reactions that occurred in the ambulatory setting and resulted in hospital admissions and emergency department visits;

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

Potential public health impact of strengthening EU pharmacovigilance

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 inappropriately. 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.

There is major potential to reduce public health burden by enhancing EU pharmacovigilance if, for example: fatal adverse reactions can be detected more quickly; if EU-wide decisions on the labelling of medicines can be taken and implemented more quickly; if effective warnings against prescribing a certain medicine to a certain at-risk group of patients are rapidly implemented; if effective warnings against prescribing together two medicines dangerous in combination are rapidly implemented; then the potential to save lives and reduce suffering is clear.

5.1.2. Overview of industry resources deployed in pharmacovigilance

Pharmaceutical companies' main post-authorisation safety activities are:

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

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;

Summary report production of aggregate post-approval adverse reactions information, including Periodic Safety Update Reports;

Safety surveillance activities, including those related to post-approval 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;

Post-Authorisation Safety Studies including safety-focused epidemiological activities;

Activities required for safety-related labelling changes; and

Ensuring that the authorities have up to date oversight of these activities

Data collected for the impact assessment

(1) The Commission services conducted a questionnaire survey of the resources (financial, human and technological) deployed by the European pharmaceutical industry in pharmacovigilance in 2005/6. The data were collected particularly in order to assess the economic burden of current EU pharmacovigilance requirements devoted to three most resource demanding activities: expedited ADR reporting, Periodic Safety Update Reports (PSUR) and post-authorisation safety studies (PASS). 83 companies responded, of which:

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

The survey covered industry with an estimated total EU turnover of € 59 billion (42% of the EU market) and an estimated total EU staff of 379,800.

A number of roundtable meetings with the industry experts were organised by the Commission services in order to better interpret data collected through the questionnaires and to quantify administrative burden cost of individual reporting obligations. Annex 2 provides a detailed overview of information on pharmacovigilance performance and resources deployed to meet the EU requirements collected from the industry; however, in summary the following key figures are informative:

- The average percentage of turnover spend on pharmacovigilance is 0.59% (inter-quartile range 0.11-0.48)

- 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 spending on pharmacovigilance can be estimated at **€832.7 million** (with a lower and upper range of €555.3 and €1124.3 million respectively).

5.1.3. Overview of regulatory authority resources deployed in pharmacovigilance

The Commission sponsored Independent study[11], as well as a survey conducted by the "Heads of Medicines Agencies, have collected detailed data on the number of staff working in the regulatory authorities on pharmacovigilance. The main relevant tasks covered by national competent authorities are data collection and data entry, data management and signal detection, risk assessment, regulatory actions, risk communication, audit and quality assessment and monitoring of compliance.

Only a small part of each agency's resources is directly dedicated to pharmacovigilance. The median proportion of pharmacovigilance staff is only 5% of the total agency staff. About two-thirds of the pharmacovigilance staff is devoted to scientific tasks. The staff profiles

11 http://ec.europa.eu/enterprise/pharmaceuticals/pharmacovigilance_acs/docs/acs_consultation_final.pdf

include scientific, medical, pharmaceutical and administrative staff. Table 2 gives an overview of human resources available at national and Community level.

The independent study has concluded that very variable and frequently insufficient resources are available for pharmacovigilance in some agencies. The independent study concluded that staff numbers at some agencies lie under a minimum required to maintain essential pharmacovigilance functions. Furthermore the independent study recommended that to fully comply with the current rules (legislation and guidelines) would necessitate the EEA National agencies employing at least 1.2 employees per 1 million of their population. At present 17 of the national agencies employ less than this number.

Table 2 Resources of the EEA medicines agencies deployed in PhV in 2004

Variable	**Total** for **30** NCA's	**Mini mum**	**25% quartile**	***Average***	***Median***	**75% quartile**	**Maxi mum**	**EMEA**
Staff total Agency	7,026	8.5	118.3	*270.2*	*170.0*	294.0	1452.0	335
PhV staff total	**317**	**1.0**	**2.8**	***11.8***	***6.3***	**11.8**	**68.5**	**27**

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

EMEA pharmacovigilance resources

As well as having certain distinct pharmacovigilance tasks, the EMEA 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.

The total EMEA budget reached €163 million in 2007. An increase of the budget over time has been covered by the fees charged to the industry (there are no fees for pharmacovigilance), while the Community contribution has remained stable over time. Fee revenue activities are estimated to further increase in the coming years in line with the general increase in the number of centrally authorised products.

The existing EMEA activities include the management of suspected adverse drug reactions in the pre- and post-authorisation phase (individual case safety reports - ICSRs), periodic safety-update reports (PSURs) and risk-management plans (RMPs). Maintenance activities relate to post-authorisation commitments (specific obligations, follow-up measures), renewal applications and annual reassessments. Pharmacovigilance and maintenance activities accounted for 13.5% of the Agency human resources (corresponding to 70 FTEs) and 14.54% of the Agency costs in 2007 (€ 25.2 million including support service).

5.2. Impact analysis of specific options

5.2.1. Clear roles,responsibilities and obligations

Making clear in the legal provisions the tasks for those stakeholders covered by the current EU legislation (given the Treaty basis for the legislation this includes marketing authorisation holders, Member States and their competent authorities, the EMEA and the Commission but not healthcare professionals and patients) would clearly delineate respective roles and provide necessary legal certainty and enforceability. Clear responsibilities would increase the robustness of pharmacovigilance and benefit to public health by ensuring that the parties know what is expected of them and by supporting inspection and audit. Greater clarity of roles and responsibility will increase industry

compliance with a consequent benefit to public health. Clarity of roles and responsibilities would also reduce duplication of effort, increasing the efficiency of the pharmacovigilance system. Including an implementing measure on Good Vigilance Practices (GVP) would ensure standards that would be used for to support processes and efficiency, as well as, quality management.

It should be noted that these options can be seen as horizontal support measures underpinning all of the other measures and processes in pharmacovigilance. Data provided by industry indicated short-term cost for companies in terms of drafting internal SOPs and training of staff at local, European and global level. Estimated resources that the introduction of these policy options would require varied from 0.2 to 1.5 FTE as one off yearly cost, respectively €17,248 to €129,360 per company. Nevertheless administrative costs for industry and regulators would not change significantly in the long-term due to minimising duplication of effort and conduct of unnecessary tasks: on the contrary clear definition of roles and responsibilities could contribute to the reduction of societal health burden of ADRs, which diminishes the true value of modern drugs.

5.2.2. Rationalise EU decision-making

For the quantitative assessment of impact, the two specific options of strengthening the pharmacovigilance committee structure and rationalising the EU referral system are considered together.

For the majority of safety issues occurring in the EU today, including serious issues relating to fatal adverse reactions, the current intergovernmental approach leads to the EMEA Pharmacovigilance Working Party informally discussing the issue and its non-binding recommendations are then implemented inconsistently by some Member States (often over a period of years). This means patients across the EU are not optimally protected from adverse reactions to their medicines, even after an issue has been considered at EU level. Rationalising the existing EU referral procedures and reinforcing the committee structure would lead to faster and more robust EU decision-making on safety. Recommendation of the new pharmacovigilance committee structure would lead to concerted safety action across all Member States, instead of scattered implementation of non-binding conclusions of the existing 'Pharmacovigilance Working Party.

Improved decision making at the EU level would subsequently result in a major benefit to public health by ensuring that important safety issues are rapidly and robustly dealt with across the EU and cost savings for industry and national regulators as safety issues will be dealt with in one coordinated, fast and robust EU procedure rather than disparate national reviews, studies and actions.

Companies are currently dealing with individual authorities which requires time for discussion on whether a drug safety action should be implemented, when it should be implemented, as well as, the content of the change to marketing authorisations and product information to be implemented. Administrative costs relating to negotiating and managing adjustments of product information (regulatory actions, translations etc.) require approximately 24 hours on average per a company for each single EU country per one marketing authorisation (€1176). This includes the whole procedure up to and including the updated Patient Information Leaflet to be available in the package. A model company estimates additional costs due to protracted implementation of safety variations between

various Member States at between €40,000 Euros to €300,000 (the later figure representing the situation where a Member State requires additional statistical analyses of safety data or analysis and update of literature reviews).

There is experience with the current referral system including the current increasing use of the specific pharmacovigilance 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 proposals will bring, we consider 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 50% of a Type II variation fee in the centralised procedure. This will represent a cost to the regulators of 20 x €36400 = €0.73 million.

The establishment of an expert pharmacovigilance committee structure would:

- Strengthen EU level of pharmacovigilance expertise;
- Ensure high scientific standards of EU level decision making on pharmacovigilance issues relating to nationally authorised products;
- Enhance EU level coordination of pharmacovigilance processes;
- Lead and support national pharmacovigilance systems in those Member States with limited pharmacovigilance resources.

The public health benefits and societal savings in qualitative terms are clear. For example, if a newly marketed medicine causes a previously unrecognised fatal adverse reaction and this is rapidly detected and found to be preventable through a risk minimisation measure, if decisions are taken rapidly at EU level (through the new referral system and committee structure with a binding Commission decision) then lives will be saved across the entire EU. Quantification of the public health benefits of the options are taken together in section 6.

In the December 2007 public consultation the Commission services proposed a pharmacovigilance committee made up of Member State representatives. Feedback from stakeholders suggested that the committee should be made up of experts not Member State representatives and that the interface with existing EMEA committees needed clarification. Impact assessment suggested that the new committee would increase costs. Therefore, the final orientation includes a smaller expert pharmacovigilance committee with clear interface with existing committees.

In addition, in the public consultation the Commission services proposed that all issues lead to an Opinion of the existing EMEA Committee on Human Medicinal Products and then to a binding Commission decision. Stakeholder feedback, including from Member States and the existing EMEA committees suggested a possible role in implementation of referral outcomes by the Member State "Coordination Group". This will reduce the number of Commission decisions necessary and maximise the use of existing EMEA and Member State resource while at the same time ensures legally binding decisions.

5.2.3. Transparency, communication and penetration of key warnings

Transparency and Communication

For the quantitative assessment of impact, the transparency and communication specific policy options are considered together. Codification of transparency and communication principles in law would clarify roles and timing of communications about major new or

changing safety issues.These communications are today frequently not coordinated at EU level leading to contradictory messages when patients access media from different Member States. At the same time civil society is increasingly asking for more openness in the operation of regulatory authorities. Although the EMEA since its establishment has taken various actions to increase its transparency, new initiatives are needed to meet the increasing demands of patients, healthcare professionals and the general public.

For major safety issues including safety issues affecting drug substances authorised in more than one Member State the EU committee structure would coordinate (but not replace) the communications of the Member States. The EU portal on the safety of medicines, set-up and maintained EMEA, would be the main platform for all announcements related to medicines safety dealt with at the EU level and would include links to websites of the Member State competent authorities. MAHs would be obliged to monitor regularly the safety portal(s) and update their product information in line with safety recommendations.

Strengthened medicines safety transparency and communication would increase the understanding and trust of patients and health professionals in the safety of medicines and the regulatory system. Clear, coordinated messages about specific safety risk issues would improve the safe use of medicines and reduce public health burden of ADRs (see Section 6). It should be noted that the final orientations include a very high level of transparency of the EMEA Committees involved in pharmacovigilance including making all recommendations public. Higher transparency is likely to increase the compliance of industry which would further benefit public health and confidence of citizens in the regulatory system. Coordinated communication of safety issues to the public across Europe and globally would enhance the credibility of a well defined governance structure and system.

The proposed transparency provisions would be cost neutral for industry. In the relatively rare event of needing to negotiate a crisis communication (e.g. Dear Healthcare Professional Communication in the event of a major safety issue), this would be with a single body for the whole EU instead of multiple national agencies would reduce the related administrative burden, which was estimated by companies as €8,000-10,000 for multiple agencies versus €1,000-6000 for single agency for initial communication.The expected savings for an MAH would be subsequently between €4000-7000 for negotiating a single communication.

The independent study indicated that NCAs employ on average 2.0 FTE staff for risk communication. Better coordination at the EU level may reduce cost for the national authorities; however any savings would be balanced by an increase in costs for transparency. In addition the EMEA and to a smaller extent also for the NCA’s will need to work on their existing websites. Increased costs for EMEA, in comparison to resources already foreseen to increase level of transparency in general, would be 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). For the Member States it is estimated that 27 additional staff would be needed to manage the websites and transparency. There will be an estimated one off cost of €1 million and annual maintenance cost €646,832 for the EMEA, respectively €3 million one off and €2.3 million annual across the Member States for technical improvements to their respective websites

Product information

The current organisation of product information makes it difficult to identify the most important safety warnings: this results in a risk that key safety measures/warnings may be missed. The proposed sections in the Summary of Product Characteristics (SPCs) and Patient Information Leaflet (PILs) on 'key safety information' would allow patients and health care professionals to rapidly identify key safety messages. There is clearly a major benefit to public health by ensuring that key safety information is highlighted maximising the chances of it being read, understood and leading to risk minimisation. Clearer key safety information and warnings in product information would improve the safe use of medicines and decrease incidence of ADR's and number of ADR related deaths and injuries and thus substantially contribute to the reduction of public health burden (see section 6 and Annex 2). However, many stakeholders in the public consultation emphasised that risk information should not be presented in isolation but be balanced with information on the benefits of medicines.

Table 3 Costs of introduction of a new section in the SPC and PIL for a model company

	Centrally authorised (50 product presentations)	Authorised through MRP (140 product presentations)
Type II variations costs	€ 1,740.000	€ 2,422.741
User Consultations for Package leaflets costs	€ 424.830	€ 728.280
Implementation costs (packaging elements re-design)	€ 156.676	€ 216.104
Total	€ 2,321.506	€ 3,367.125
Grand total (CP + MRP)	**€ 5,688.631**	

Assuming that the 'key information' section will need to be added to all SPCs and PILs of existing products, and that, if these are implemented immediately, Type II variations to marketing authorisations will be required, then the cost for fees, user readability testing and regulatory time for industry would be substantial without a transitional period, and this is illustrated with the example of a larger innovative model company in Table 3. Review and approval of labelling variations for thousands of licensed products would also create a substantial administrative burden for regulatory agencies, although this would generate fee income. It should be noted that simplification of the variation system in the EU is in the subject of a separate legislative proposal.

Implementation costs are expected to be significantly less if staggered over 5 years since packaging and package leaflet changes would normally occur during this period for the vast majority of marketed products.

Our analysis suggests a substantial positive public health impact of the introduction of a new section in the SPC and PIL. However impact assessment and stakeholder feedback revealed that changing product information will lead to significant industry and regular costs but that these can be minimised through delayed implementation. Stakeholders also suggested that highlighting safety information without putting it into the context of benefit could reduce patient concordance with therapy. Therefore the final policy option chosen is

staggered introduction of key information sections (i.e. benefit and risk information) in the Summary of Product Characteristics and Patient Information Leaflet.

5.2.4. Company pharmacovigilance system

The current requirement to submit with the market authorisation a "detailed description of the pharmacovigilance system" was introduced in November 2005 and represents a major administrative burden for industry and regulators because any change to a company system has to be notified through a variation to the marketing authorisation (for each individual product and each national authority). Therefore if the industry is compliant, a minor administrative change in a company's pharmacovigilance system necessitates hundreds of variations to marketing authorisations in the Member States, which obstructs companies from having a modern, flexible pharmacovigilance system.

Replacing the current system by a summary submitted to the authorities at authorisation with the introduction of a "Pharmacovigilance System Master File - PSMF", a detailed file on the company pharmacovigilance system maintained by companies in their offices, would simplify informing the authorities about the company pharmacovigilance system. This would free up resources and would eliminate the current situation where industry avoids change or is non-compliant (to avoid the administrative burden). Overall the same level of oversight by the authorities would be maintained as 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.

Average current costs of a Type II variation for changing the PV system of a model company:		
Overall Regulatory cost for preparation	=	€ 125,000
Fees for Type II variation in CP € 72,800 x 16 products	=	€ 1,164,800
Fees for Type II variation in MRP € 50,000 x 20 products	=	€ 1,000,000
Total per company:		**€ 2,289,800**

The introduction of the PSMF would reduce the administrative burden to industry and regulators from frequent variations to marketing authorisations. Considering the substantial costs related to frequent Type II variations there will be major costs savings for industry. Based on industry consultation we can assume that 0.25 FTE is sufficient to make and maintain Pharmacovigilance System Master File. Furthermore, assuming two changes per year to a company's pharmacovigilance system which would no longer require a Type II variation the introduction of Pharmacovigilance System Master File would result in potential € 4.4 million net reduction of administrative burden for a single company.

Table 4 gives an estimate of potential costs, based on sample data provided by the industry, of all variations due to change to a company PhV system for centrally authorised and mutually recognised products since November 2005 (when this requirement was implemented) considering full compliance of companies with the legal requirements. On the other hand this number provides a conservative cost estimate as it does not include nationally authorised products and does not adjust for the increase of newly authorised products over time (i.e. the numbers increase steadily in the no-change scenario).

Table 4 Notification of Change to a company PhV system: cost estimate at the EU level

	Cost per 1 variation	Changes per year	**Products affected**	**Costs of variations**
Centrally authorised	€ 72,800	2	125	€ 18,200,000
MRP+DCP	€ 50,000	2	677	€ 67,700,000
Total costs				**€ 85,900,000**

Suggestions by industry during the second public consultation to have Pharmacovigilance System Master Files held at and validated by EMEA were rejected on the basis of burden on EMEA and subsidiarity for small companies operating in only one country.

5.2.5. Ensure proactive and proportionate colleaction of high quality safety data

Risk management planning and post authorisation safety studies

Because they are so closely interlinked the three specific policy options falling under this heading are considered together. Strengthening of the role of risk management planning would make safety monitoring and risk minimisation, driven by the knowledge of the safety of a product, more proactive and would base decision-making on more robust data. Clarification of the legal requirement to submit a risk management plan with a marketing authorisation application and inclusion of any key risk management measures in the marketing authorisation would make certain that MAHs conduct the measures specified (i.e. were compliant). The measures would also ensure that MAHs would provide updates on risk management plans to the competent authority and the EMEA at specified times. The legal basis for requesting risk management plans for authorised products when there is a public health concern would also be clarified making these important public health tools legally enforceable but proportionate. The regulatory assessment work for risk management plans relating to new medicines would be covered by the existing fees charged for marketing authorisation applications. For medicines already authorised it is proposed that new risk management plans would attract an industry fee and this is detailed in Annex 2.

This option would improve and strengthen the monitoring of the safety of medicines so that safety issues are rapidly detected, and effectively dealt with based on more robust data. These changes will be a major benefit to public health by ensuring that safety evaluation of products is prospective (i.e. based on risk management planning) and by ensuring that high-quality safety studies are conducted (i.e. there is compliance) when justified by safety concerns.

Post-authorisation safety studies form an essential part of risk minimization activities and already involve substantial industry resources. Their unit cost ranges from €10,000 for a small observational study to millions of Euros (e.g. the Antiretroviral Drug Pregnancy Registry maintained by a consortium of companies costs €1,300,000 per year).

Based on the 2006 industry 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) it 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%.

The proposals include codification of guiding principles for the conduct of non-interventional post-authorisation safety studies, i.e. safety studies of marketed products that are not clinical trials, initiated, managed, or financed by the marketing authorisation holder and that involve collection of data from healthcare professionals or patients. The oversight would be by NCAs or, if conduct is in more than one Member State, by the EU pharmacovigilance committee structure in order to ensure that non-interventional post-authorisation safety studies have health rather than promotional objectives (see section 6 for quantification of benefit to public health)

The impact on the Member States for this oversight would be variable. Some Member States have national legislation in place and already scrutinise study protocols while in other Member States there is no oversight. The cost to the EMEA of administering the oversight by the new committee structure would depend on the number of studies submitted. The number of studies 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. At national level there would be an additional 12 FTEs needed in order to assess the PASS protocols on behalf of the EU. These rapporteurship activities would be reimbursed from collected fees.

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 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.

Any additional investment into proactive data collection or risk minimisation measures should be outweighed by an increased public health benefit. Robust, proactive pharmacovigilance with key measures included as conditions of marketing authorisations of products could also lead to earlier product authorisation providing faster return on investment and, by reducing the cost of capital (borrowing costs being a significant part of the total) the total cost of product development is reduced. Although estimates vary (depending on how costs are calculated and the assumptions included) it is suggested that it costs to the tune of €1 billion[12] to get a product to market. Considering the limited period of patent protection, each 1 month of delayed market access results in an increased cost of capital and due to lost or delayed return on investment. According to a study conducted by the Tufts Center for the Study of Drug Development, quicker approval of new drugs by the US Food and Drug Administration has not increased the number of prescription drugs withdrawn for safety reasons in the US. In this manner robust pharmacovigilance drives

[12] Tufts Centre for the study of drug development (CSDD), May 2003

innovation by increasing confidence and reducing costs and also supports earlier access of new medicines to fulfil patients' unmet medical needs[13].

Based on the results of the public consultation the detailed provisions on risk management plans were changed. The proposal that went to public consultation in December 2007 suggested that entire risk management plans would be annexed to the marketing authorisation. However, stakeholders pointed out that this would result in important questions of compliance as risk management plans can be very detailed. Therefore in the final orientation only key elements of risk management plans will be annexed to the marketing authorisations and therefore be legally binding.

In the draft proposals which were the basis of consultation in December 2007 it was proposed to limit the authorities objection criteria to non-interventional post-authorisation safety studies being promotional or if the study was considered to be a clinical trial. However in the consultation there was a clear call from stakeholders for oversight to ensure that studies have a scientific / public health objective and the final orientation contains this additional objection criteria.

Simplification of adverse drug reaction case reporting

The input of pharmacovigilance is to signal a potential safety concern, using data from single case safety reports, the literature, clinical trials, epidemiological studies and other data sources. Adverse drug reaction (ADR) Single Case Safety Reports (ISCR) are a backbone of the input step of pharmacovigilance.

The option foresees that the EMEA will operate a truly European database of ADR reports, accessible to all the Member State medicines authorities. Simplification of the rules based on electronic reporting with full utilisation of modern information technology would establish a single reporting point for all MAHs irrespective of the licensing route, reducing significantly administrative burden of ADR reporting and freeing up resources for both industry and regulators, which can then be reinvested into efforts more closely linked to health protection and promotion.

Table 5 Number of Individual Case Safety Reports in the EU in 2004

Variable	Total for 30 NCA's	Mini mum	25% quartile	*Average*	*Median*	75% quartile	Maxi mum	EMEA
ICSRs in databases total	1,619,858	64	1,398	*64,794*	*20,000*	57,254	522,254	N.A.
ICSRs received in 2003	95,311	0	328	*3,666*	*1,073*	4,256	19,248	N.A.
ICSRs received in 2004	100,036	26	318	*3,848*	*1,406*	4,819	20,116	N.A.

Source: Fraunhofer study, 2005

Companies estimate the administrative cost per ADR report at about €200. Data from industry indicates possible savings from the current duplicative reporting requirements to reporting to the EU database only as ranging from €100 to €130 per report.

[13] Independent study conducted for the Commission by Charles River Associates and available at http://ec.europa.eu/enterprise/pharmaceuticals/pharmacos/docs/doc2004/nov/eu_pharma_innovation_25-11-

Case study: Medium size company

35 FTE PhV staff, spending anually €1,050,000 on PhV activities:

Costs of 1 ICSR reported both to individual member states and Eudravigilance *(current situation)*: **€150 – 250** per ADR

- vs. to Eudravigilance only (*proposed option*) **: €70-100** Euros Per ADR
- vs. to Eudravigilance and the only MS where the ADR occurred (alternative option): €90-120 Euros per ADR

Large Company:

Total costs related to ADR reporting on a yearly basis, based on 31,500 unique reports a year

- Administration costs: Savings = € 156,000 / year.
- Current workload 3 FTE – Expected workload with new legislation 0.5 FTE – Saving: € 375,000 / year

Total savings: € 531 000 / year

The total costs to the industry as a sector can be extrapolated to €299.0 million based on the 2006 survey data and the number of companies operating in the EU. On the basis of individual companies data given in Table 6, the median savings for the industry was estimated at 25.8% and thus that this option will save the industry €77.1 million per year. As the proposal will ensure that all the authorities and all relevant companies can access the ADR data via the EU database, public health protection will be maintained and may even be increased by freeing up resource currently expended by some national agencies on single case handling (see impact on national agencies in section 6).

Table 6 Estimated savings due to rationalised ADR reporting

	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%**

During the December 2007 public consultation some regulators suggested that companies should report EU domestic cases to Eudravigilance and the EU country of origin. However, this was rejected on the grounds of impact as 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.

The December 2007 public consultation proposed that all ADR cases be reported within 15-days by the industry including non-serious EU cases. Stakeholders pointed out that this would result in a 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). Depending on a cost model per case, the proposed obligation to send non-serious EU cases on an expedited, rather than on a periodic basis, would generate a number of additional expedited submissions and increase administrative burden in comparison to their periodic electronic reporting. Therefore this sub-option was not pursued.

The current EU Telematic Plan foresees development costs for the Community pharmacovigilance 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 (see section below on impact on overall telematics budget). Additional staff of 10 FTE for running the collection and management of pharmacovigilance 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.

Scanning of the scientific literature

Scanning of the scientific literature and entering case reports from the literature on Eudravigilance by the EMEA would avoid the duplication currently conducted by the industry and national regulators and thus generate major cost savings for those stakeholders.

Based on industry data, the potential saving for a model large company would between €500,000 and 1 million. This option would benefit public health by freeing up resource for both industry and regulators which can then be reinvested into efforts more closely linked to health protection and promotion. Furthermore, by reducing the number of duplicate ADR reports in the EU pharmacovigilance database it would improve the quality of pharmacovigilance data available.

Estimated current ***costs of company's screening the published literature*** for ADRs

Number of products covered by this screening = 64

- Internal screening = 3 FTE
- External Literature screening costs (2007) = 412 000 Euros.
- Internal data entry and submission of literature reports = 800 X 450 Euro = 360,000 Euro

Nevertheless, 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. Based on the public consultation, the EMEA role would be limited to off-patent drug substances therefore particularly benefiting generic and OTC companies. It is very difficult to accurately extrapolate the cost savings to these specific industry sectors due to the diversity of economic operators and the fact that some sectors of the industry are already collaborating on literature monitoring to save costs (e.g. a German industry association coordinating efforts to reduce costs). However, it is reasonable to estimate that the savings to the industry sector from centralising this important part of literature monitoring would exceed €10 million.

On the basis of estimates from the EMEA (3 additional information analysts if the main function was outsourced) and from one private literature monitoring company[14] (€530,000 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. It should be emphasised that the final orientation

[14] Wolters Kluwer Health

provides for a flexible approach with the EMEA literature monitoring focussing on established drug substances. This evolution of the policy option is based on the feedback of the EMEA, national regulators and industry regarding the impact of earlier draft proposals.

Medication errors

There is no accepted definition of a medication error, however, the term may include prescribing, dispensing or administering the wrong medicines to the wrong patient at the wrong dose, by the wrong route, at the wrong time or in combination with the wrong co-medication. Product related causes (rather than human causes) of medication errors include sound-alike or look-alike drug names, similarities in the outer appearance of medicines' packages and labelling as well as unclear, ambiguous or incomplete labelling information (see section on Transparency and Communication). It should be noted that, according to the medical literature, 30.3% to 47.0% of adverse drug reactions caused by medicines in hospital settings appear to be consequences of medication errors and therefore may be considered as preventable.

Medication errors likely represent the most common single preventable cause of adverse events. The Council of Europe Medication Safety Report recommends Member States to establish medication errors reporting systems as a component of or to complement patient safety incident reporting systems for incidents involving medicines. Such systems must include primary care as well as hospital settings and should be developed at local, national and European levels.

Changes in the current proposal on medication errors are limited in scope and are informed by and complementary to the action being developed by DG SANCO of the European Commission (Council Recommendation on patient safety and quality of health services, including the prevention and control of healthcare-associated infections).[15] The pharmacovigilance package proposes to clarify that companies receiving a medication error report should report this to the European Pharmacovigilance database and that the Member States should ensure that such reports are exchanged between the national competent authority for medicines and any national authority for patient safety. By placing this legal obligation on the Member States to exchange data, convergence in the use of terminologies used for reporting (currently MedDRA for pharmacovigilance) and of policies for 'blame free' reporting will be enhanced. The proposals do not directly impact on how the Member States collect such reports from patients or healthcare professions. The proposals will benefit public health by ensuring that the data on medication errors that cause adverse reactions are available to all the relevant authorities thereby allow any necessary action be it product related (covered in the pharmaceutical legislation) or healthcare system related (covered by Member State rules).

No significant additional costs for authorities are foreseen from the proposals as the requirements are simply for data exchange. This option should not affect industry cost as most companies indicated that they are already recording ADRs in their database independently on the dispensed dose and healthcare circumstances.

[15] http://ec.europa.eu/health/ph_overview/patient_safety/consultation_en.htm

It should be noted that no definition of the term "adverse event" appears in the proposals therefore any such definition to be used in the forthcoming patient safety proposal will not be in conflict with this pharmacovigilance legislative proposal.

Periodic Safety Update Reports (PSURs)

During the 2006 round of public consultation both regulators and industry emphasised that there is a lack of correlation in the current legal provisions between the PSUR reporting requirements and the risks posed by the product. This leads to expending major resource by industry and regulators on PSUR production and assessment with questionable public health benefit.

Stakeholders also pointed out that removal of the routine requirements for uncoordinated submission of PSURs for older products would eliminate duplication of reporting to different national authorities and duplication of their assessment. For instance, currently hundreds of companies have authorisations for paracetamol products and produce hundreds of periodic reports which are submitted to the 30 EEA Member States. In 2004 over 17,000 PSURs were received by NCAs. It can be assumed that many of these were assessed on multiple occasions by different Member States, without additional benefit to public health from this duplication of effort. Indeed, by taking scarce resource, this duplication may reduce public health protection. A pilot project on assessment work-sharing has been recently launched by the Heads of Medicines Agencies (HMA) and EMEA Pharmacovigilance Working Party on a voluntary basis and seems to go well so far. However, first experience shows that a clear legal basis for this exercise is needed, as difficulties of enforcement are encountered.

Currently harmonised birth dates have been agreed (allowing submission of PSURs to all Member States at the same moment) for about 650 substances. The innovator PSURs frequently have different reference dates (data lock points) in the different Member States, because of different authorisation dates. The three European pharmaceutical trade associations are finalising proposals for harmonised birth dates for a further 1000 substances. This would result in submission of 1650 PSURs over three years, which would mean 550 PSURs per year. This differs considerably from the 17,000 per year submitted currently.

If we use the current informal work sharing 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 PSURs. The data provided by pharmaceutical companies suggest reduction of their submission of between 10 and 100% (depending on the company category). The following model presents a detailed cost breakdown for a model mid-size company:

Following activities / Steps are involved in the preparation of PSURs:			
Quarterly Schedule		Information Request	
Information Compilation		Line-listing	
Literature Review		PSUR Authoring	
PSUR Compilation		PSUR Medical Review	
PSUR Distribution		Submission to Authorities	
Product Safety Committee			
Response to Questions			
Case study (a model company)			
Number of PSURs per annum:			120-140 / Year
Staff deployed to meet EEA PSUR Obligations:			10
Cost to meet EEA PSUR Obligations:			€770,000
(this excludes cost of external literature searches, safety database, training and overheads)			
Estimated cost savings following the proposed provisions			
-30% Less activities	:	4 (staff)	= 230,000 Euros

While the proposed reduction will not affect innovative medicines with an evolving risk/benefit profile, representing about 10% of marketed products, the frequency of PSUR submission for well established products could be halved (assuming average submission frequency 6-yearly instead of 3-yearly currently). On this basis, the saved resource for industry, mainly generic and OTC producers, is estimated at 38% of the current cost (as these PSURs are usually smaller), and this corresponds to an estimated saving of €72 million for the industry sector per year.

However, innovative companies are in many instances producing continuously updated versions of PSURs depending on the different data lock points in the different Member States. Theoretically this can be up to 27 updated versions in three years (27 Member States). According to the Commission's proposal this will be reduced to one electronic submission to the EMEA and thereby distribution to the relevant regulators. If we assume that the mean number of versions of a PSUR in the EU is currently 13 (PhVWP data) then this additional reduction in workload for industry is substantial. Figures in Table 7 contain costs related to administrative tasks related to the submission of the reports to the authorities. They do not include savings resulting from the preparation of one PSUR in a single format to all Member States at the same time.

Table 7 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 structure 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**

The reduction in the number of PSUR assessments for NCA's is clear and the workload is further reduced through worksharing between Member States. This will benefit public health by by reducing duplication of effort and freeing up resource. However, there will be considerable work required to support the EU PSUR work-sharing, including assessments that will be considered at EU level and made public. Therefore overall any resource saving from reduced duplication is likely to be absorbed by increased quality of assessment.

By having coordinated EU assessments of the reports with recommendations for the product information placed on the EMEA web-site and requirements for companies to keep their product information up to date, there will be faster product safety assessment and faster updating of product information, thereby getting warnings to patients faster, so benefiting public health. From a public health point of view harmonisation of safety information in SPCs and PILs for the same drug substances is important. It is not possible to explain to EU citizens that the safety information in patient information leaflets differs between similar products and across borders, which is frequently the case today.

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.

5.2.6. Involve stakeholders in pharmacovigilance

Patient reporting

The current EU legislation does not include provisions for reporting of adverse reactions by patients themselves. However, patient behaviour has been changing given their increasing access to information and empowerment, and some Member States have taken initiatives in favour of patient reporting. For instance in Denmark, new legislation came into force on 1 July 2003 allowing patients and their relatives to directly report adverse reactions to the competent authority. In the same year, also in the Netherlands the national reporting system started offering an internet-based reporting mechanism for all patients. Some other Member States initiated pilot projects to explore potential mechanisms for direct patient reporting and their value as a source of safety information.

A number of positive experiences have been reported from several Member States regarding consumer reporting of ADRs, which could have particular utility for OTC medicines. According to the EMEA Pharmacovigilance Working Party report, in Denmark, around 150 reports have been received yearly by the competent authority since 2003, while in the Netherlands the reporting rate has reached about 820 per year. Through the programmes in France and Sweden, about 250 and 200 reports respectively were collected by the competent authorities. France specifically collaborated with 22 patient organisations. In the UK, 6000 reports were collected through the extended yellow card system between 2005 and 2007, translating into an average reporting rate of 200 per month (via paper, telephone, internet).

The quality of the patient reports is often very good and was overall judged as beyond expectations. 75% of the French reports were deemed valuable for further assessment. In the Netherlands, patients provided more details than healthcare professionals on outcome

including non-recovery, and there was also more information on the actual use of suspected medicinal product as well as of over-the-counter products. Likewise, UK patient reports included more information on the impact of adverse reactions on quality of life. In Sweden, patient reports were perceived as an additional source for information on over-the-counter products as well as of drug misuse. They also saw a 100% responder rate when contacting patients for more information. In France, 11% of patient reports were submitted with medical documentation and for about a further 20% a medical confirmation was obtained through follow-up with the physician as permitted by the patient.

In the Member States with a nationwide direct patient reporting option, a considerable percentage of all adverse reaction reports originate from patients: In Denmark this percentage is 7%, and in the Netherlands it has reached 20%. Also companies are already receiving a significant number of reports from patients, which represent about 40% of all reports in their worldwide databases (from 5% to 70%). Empowering patients to report their side effects will increase their confidence in safety monitoring and the safety of medicines in general.

In the public consultation the Commission services proposed that patient reports for new medicines be processed by the industry and then submitted to the European database (to reduce the workload impact on the NCAs) and for old medicines NCAs offer web-based reporting. However, stakeholders including NCAs have indicated that they wish NCAs to receive these reports directly.

In 2004, 55 employees (adapted from the Independent study) were tasked by entering adverse reaction reports in the EEA national medicines agencies. Assuming that patient reporting is mainly via the web (thus minimising the need for data entry in the NCAs), and assuming that the increase in number of non-industry reports received is 50 % of the current total number received by NCAs directly (this is considered a maximum) the increase in staff needed by the NCA to process these reports can be estimated at 15 FTE for the entire EEA. However, the overall impact on ADR processing resources of the proposals is likely to be neutral as there will be a corresponding decrease in reporting by the industry directly to the National authorities. In this way the national authorities will be able to focus their resource on the reports directly received from their citizens rather than reports already processed by industry, which would nonetheless be available to them for data analysis via the EU pharmacovigilance database.

6. COMPARING THE OPTIONS

Legend for table 8 : *the relative strength of an impact is qualified as:*

- Positive: "slight", "moderate" and "high" (+, ++ or +++);
- Negative: "slight", "moderate" and "high" (-, -- or ---);
- Neutral / No effect: 0
- Particular impact on SME: SME

6.1. Overview of social and economic impacts of chosen options

Table 8 gives a qualitative overview of the social and economic impacts of the chosen specific options (either originally proposed or revised on the basis of impact analysis in section 5) assessed against existing provisions, i.e. "No policy change" option. The relative strength of an impact is qualified according to the available data, the feedback from stakeholders or available literature references.

In summary, all analysed specific policy options have either positive or neutral impact on public health protection. Secondary public health criteria are also assessed qualitatively in Table 8, these being public confidence and facilitated access of citizens to innovative medicines by supporting the post authorisation monitoring of medicines. Again, none of the specific policy options had a negative impact on these public health criteria.

In addition the scale of economic impacts that has been identified, ranging from a clear reduction of administrative burden to tangible implementation costs, is quantified in section 6.2. These were carefully considered in the context of their public health benefits and in some cases revised to achieve the best cost-benefit ratio.

No major negative environmental impacts of the proposals were identified. However, it should be noted that minor environmental benefits from the legislative proposals can be identified compared to the status quo, these being:

- Through greater coordination and use of information technology there will be a dramatic reduction in paper based reporting and duplicative reporting of individual case and periodic safety reports.

- The new transparency rules will ensure wide access to assessments on pharmacovigilance some of which may be relevant to the assessment of environmental risk.

Enhanced implementation and enforcement work within the current legal framework (i.e. option 1) will improve pharmacovigilance and EU public health protection and it is for this reason that work to improve implementation of the current EU pharmacovigilance system is an integral part of the Commission "Strategy to Better Protect Public Health by Strengthening and Rationalising EU Pharmacovigilance" announced in February 2007. However, the impact overall of improvements of the current EU system will be limited and the step change improvement in public health protection can only be realised with a change to EU legislation. On this basis only option 4 proved a realistic way of meeting the objectives proposed.

Table 8 Qualitative overview of social and economic impacts of the pursued options

	SOCIAL IMPACTS			ECONOMIC IMPACTS						
Analysed options (revised if applicable)	Public health protection	Access to innovative medicines	Public confidence	Public health burden	Industry One-off	Industry Ongoing	EMEA One-off	EMEA Ongoing	NCA One-off	NCA Ongoing
Codified roles and responsibilities	++	+	+++	++	-	0	-	0	-	0
Clear committee structure	+++	+	++	+++	0	+	-	---	0	0
Rationalised EU referral procedures	+++	+	++	+++	0	+	-	---	0	0
Drug safety transparency	+	+	+++	++	0	+	-	-	-	-
EU coordination of drug safety communication	++	+	+++	++	0	+	-	--	-	-
Transparency – Improved product information	+++	0	+++	+++	-	-	-	-	-	-
Company Pharmacovigilance System Master File	0	0	0	0	0	+++	0	0	0	0
Clear basis for risk management plans and studies	+++	++	+++	+++	-	--	0	0	0	0
Oversight PASS	+	0	+++	+	-	-	-	--	0	-
ADR Reporting simplification (incl. by patients)	+	0	+	+	0	+++ (SME)	--	--	0	0
Literature screening by the EMEA	+	0	+	+	0	+++ (SME)	0	--	0	0
Data sharing for medication errors	++	0	+++	++	0	0	0	0	0	0
Removal of routine requirement for certain PSURs	0	0	0	0	0	+++ (SME)	--	-	+	+
PSUR Assessment Worksharing	++	0	+	+	0	++	0	--	0	+
Legal basis for patient's reporting	++	0	+++	+	0	0	0	0	-	-

Specific options, chosen for the legal proposal, providing the best sum of the impacts and an overall coherence of the EU regulatory system are:

- Clarification and codification of the tasks and responsibilities of involved parties and establish standards;
- Establishment of a clear EMEA committee structure for pharmacovigilance scientific assessment and decision making on the safety of medicines at the EU level;
- Rationalising of the EU pharmacovigilance referral procedures;
- Increasing drug safety transparency;
- EU coordination of communication about major new or changing safety issues and establishment of an EU portal on the safety of medicines;
- Introduction of a new section in the Summary of Product Characteristics and Patient Information Leaflet on ‘key information' with a transitional implementation period;
- Introduction of "Pharmacovigilance System Master File";
- Provision of a clearer legal basis for risk management plans for new and authorised products with safety concerns, including post-authorisation safety studies;
- Codification of guiding principles and oversight for the conduct of non-interventional post-authorisation safety studies;
- Simplification of ADR reporting using the EU Eudravigilance database as a central tool;
- Scanning of the scientific literature by the EMEA with a clearly defined scope;
- Exchange of data on medication errors that result in an adverse reactions including between the competent authorities for medicines and patient safety;
- Removal of the current routine requirement for PSURs for low risk, old and established products;
- Provision of the legal basis for the new EMEA pharmacovigilance committee structure to coordinate assessment of PSURs and make recommendations for product labelling.
- Provision of the legal basis for patients to report suspected adverse drug reactions;

A large number of potential policy options were highlighted by the independent study and by stakeholders during the first public consultation. The specific policy options were selected and modified based on an iterative process of problem investigation, process understanding, expert dialogue and stakeholder consultation with options being fine-tuned while others were excluded during the process. The fifteen specific policy options listed above were selected on the basis that they provided the best sum of the impacts and an overall coherence of the EU regulatory system (see Annex 3 for evolution of the policy options).

6.2. Financial impact of the chosen options

As outlined in Section 5.1, key economic impacts were measured in terms of public health burden, industry impact and medicines regulators impact. Detailed analysis is provided in Annex 2.

6.2.1. Reduction of ADR economic burden by strengthening EU pharmacovigilance

A revised pharmacovigilance system should lead to an improvement in the health of European citizens, through:

- reducing mortality (prevented deaths),
- reducing morbidity, sick leave days and impaired days,
- reducing potential disabilities,
- reducing number of hospital stays and out- patient care.
- improved access to safe medicines for unmet medical needs

From Table 9 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 hospitalization lead to delayed time to discharge. In one study, on average, each event caused 2.2 days longer hospitalization time compared with matched controls. Two other similar studies found ADRs to cause 1.91 and 3.5 extra days of hospitalization.

Another study has highlighted the public health importance of ADRs by estimating that ADRs caused over 100,000 hospital deaths in the United States in 1994.[16] This would correspondent to **197,000 hospital deaths** (142,000 if the lower confidence limit was used) when extrapolated to the EU-27 population in 2006. While each study has its own strengths and weaknesses in terms of methodology, overall the literature provides compelling and consistent evidence of a major public health burden from ADRs.

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

Table 9 Incidence and prevalence of adverse drug reaction reported in the literature[17]

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).

The annual societal economic burden of ADRs occurring in the Community was estimated at €79 billion. Acknowledging that many ADRs are caused by intrinsic characteristics of pharmaceutical substances or by patient behaviour which cannot be influenced by legislation, medical literature suggests that at least 30% of ADRs are preventable. The assessment has assumed the combined potential of the package of measures to reduce public health burden by enhancing the EU PhV system, including early detection of fatal adverse reactions, fast implementation of EU-wide decisions on the safety labelling of medicines, clear warnings not to prescribe a certain medicine to a certain at risk group of patients or not to prescribe together two medicines dangerous in combination, to be 10% of preventable ADRs in an optimistic scenario and 1% in a conservative scenario.

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

Table 10 Potential reduction of direct societal economic burden related to ADRs in the Community

Cost of prolonged hospitalisation due to preventable ADRs	€ 2,165,760,050.8
Cost of preventable hospital admissions	€ 2,571,128,886.9
Preventable burden of induced ambulatory care	€ 18,960,000,000.0
Total costs of preventable ADR's (i+ii+iii)	**€ 23,696,888,938**
Potential public health burden savings due to strengthened EU PhV	
Conservative scenario (1%)	€ 236,968,889.38
Optimistic scenario (10%)	€ 2,369,688,893.8

Table 10 shows that the package of proposed measures would reduce the economic burden of ADRs by between €0.237 and €2.37 billion. We do not monetise the value of the life of a citizen saved. However it can be 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.

6.2.2. Impact on industry

According to Eurostat data 3700 companies were involved in the production of pharmaceutical preparations in the EEA in 2005 with a total turnover of €169.5 billion. 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, the volume of the Community pharmaceutical market can be estimated at €140.7 billion.

Sixty companies provided, within the framework of the questionnaire survey, both data on their annual EU turnover and on their EU pharmacovigilance costs. These companies had a total EU turnover of €59.0 billion, representing 42% of the total EU market. Based on an extrapolation, the total annual industry resources deployed to meet the EU PhV requirements (scientific + administrative) are estimated at €833 million (with a low range estimate of €555 million and high range estimate €1.12 billion). Table 11 gives a breakdown of industry resources for key PhV activities.

Table 11 Estimated industry resources to meet EU PhV requirements (total EU sector)

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

Table 12 summarises the impact of the chosen options with major economic impacts on the industry as outlined in the section 5. 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 SME's the most. Part of these savings

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 annual savings of €145.2 million for the industry sector. For some minor impacts it was not possible to extrapolate to the whole sector and these are assessed qualitatively in section 6.1.

Table 12 Quantification of total economic impacts on the 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**

Overall, improved and robust EU pharmacovigilance system with clear legal provisions will lead to 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.

6.2.3. Impact on regulators

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. 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.

Table 13 summarises major economic impacts on the EMEA and national regulators (national competent authorities of 30 EEA Member States). The calculations estimated a one-off increase 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 additional FTEs needed in addition to the current Agency staff dealing with PhV (increase of 38%) and just over €1 million annually to outsource literature monitoring. It should be noted that the EMEA annual cost includes payment of rapporteurs in the EU pharmacovigilance committee structure of €5.3 million annually (see Annex 2 for a detailed costs breakdown)

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 13 Major economic impacts on EMEA and national regulators

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**

All monetary values are expressed in Euros.
**Re-programmed from existing telematics budget.*

The costs outlined above would not impact on the EU budget. This is because 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, although fees are suggested at Annex 2 and presented in the Financial Statement, given that the EMEA budget is currently in surplus, the size of any EMEA fee increase will have to be judged nearer the time of entry into force of the new legislation.

6.3. Highlight trade-offs and synergies

Modernisation of Directive 2001/83/EC and Regulation (EC) No 726/2004 in line with scientific progress, societal changes and emerging technologies proved to be the best option to achieve the pursued objectives. The chosen specific options convey synergy between the objectives to be achieved, i.e. increased protection of public health and at the same time redirecting resources from meeting duplicative administrative requirement to genuine risk minimisation activities. This balance is crucial to ensure that simplification would not lead to a situation where human health could be compromised. This objective is in line with ongoing international harmonisation processes and was fully supported by stakeholders, who put emphasis on the need to strengthen and simplify current provisions as soon as possible.

Legislative technique

During the first round of public consultation a significant proportion of industry responders suggested that it would facilitate the conduct of pharmacovigilance to have one single stand-alone EU regulation. This would reduce the possibility for Member State divergences in the implementation and operation of pharmacovigilance and mean that affected stakeholders would only have to refer to a single legal text. This was carefully considered during the development of the proposals, particularly its feasibility in terms of legal technique and legal drafting. However, the option of a single pharmacovigilance regulation was rejected because:

- The existing legal framework for the regulation of medicinal products is based on a directive and a regulation of the Council and the Parliament and these cover not only pharmacovigilance but also the manufacture, authorisation, supervision and advertising of medicinal products. There is an important interplay between the two legal acts which would be severely compromised by the introduction of a stand alone pharmacovigilance regulation.

- A directive (Directive 2001/83/EC) is already the basis for the EU regulatory system for medicinal products and the Member States are critically involved in the operation of the established procedures for the manufacture, authorisation, supervision, pharmacovigilance and advertising of medicinal products.

- Those requesting a stand alone regulation were considering pharmacovigilance as a narrow subset of the regulatory activities relevant to the safety of medicines. However, the specific policy options included in the final Commission proposals cover a broad spectrum of measures designed to improve the protection of public health. They are in line with the definition of pharmacovigilance provided by the World Health Organisation and impact on legal provisions throughout the existing directive and regulation. To introduce a stand alone regulation would therefore have required very complex cross referencing.

- To move all the provisions included in the Commission proposal into a stand alone regulation would therefore undermine the coherence of the existing EU legal framework for pharmaceuticals.

7. MONITORING AND EVALUATION

7.1. Monitoring indicators and arrangements for ex-post evaluation

As the proposal consists of a modification to the EU legislative framework for pharmacovigilance and this includes a Regulation and a Directive of the Council and the Parliament (Directive 2001/83/EC and Regulation (EC) No 726/2004), the first parameter to monitor will be the implementation of this new framework notably transposition by the Member States and establishment of the new pharmacovigilance committee structure by the EMEA. The Commission has established mechanisms for working with the Member States to monitor transposition and in the pharmaceutical sector the Commission's Pharmaceutical Committee is a key forum for exchanging information in this regard.

With regard to *ex-post* evaluation of the operational objectives:

The objective of making clear the respective roles and responsibilities and minimising duplication of effort can be evaluated by:

- The proposals foresee a regular report by the European Commission on the operation of pharmacovigilance by the Member States based on regular reports by the Member States themselves,

- The proposals foresee pharmacovigilance inspections of the industry and the reports of these inspections are collated by the EMEA which can be evaluated,

- The proposals foresee EMEA audit of its pharmacovigilance function being reported to the EMEA Management Board (where the Member States, civil society, Parliament and Commission are represented)

The objective to strengthening the rules on transparency relating to pharmacovigilance can be evaluated by:

- The number of Member States maintaining medicines safety websites

- The launch of the EU safety web-portal by the EMEA,

- The inclusion of information from committees, studies, PSURs, and risk management plans on the EU safety web-portal,

- The number of requests from the public for data from the EU safety database (Eudravigilance).

The objective to increasing the penetration and uptake of specific risk minimisation warnings can be evaluated by:

- Collecting a sample of EU product information 5-years after the legislation enters into force to measure the proportion of products having a 'key information' section included.

The objective to simplify the existing requirement for a 'detailed description of the pharmacovigilance system' can be evaluated by:

- Measuring the proportion of Pharmacovigilance System Master Files at inspection of companies, and there quality (available in inspection reports collated by the EMEA).

The objective to clarify the legal requirement to conduct post-authorisation safety studies including those in risk management systems can be evaluated by:

- Using the existing EUDRACT database on clinical trials, measure the number of clinical trial applications submitted that meet the definition of a post authorisation safety study,

- Measure the number and quality of risk management plans submitted,

- Measure the concordance between the studies required in risk management plans and studies conducted (via PSURs and risk management plan updates),

- Measure the number of non-interventional study protocols submitted.

The objective to rationalise and simplify the reporting of suspected adverse drug reactions (ADRs), through both expedited and periodic reporting can be evaluated by.

- Measuring the number and quality of ADR reports submitted to the EU database and analysed by source (including the proportion from patients),

- Measuring the number and quality of PSUR reports submitted and the number of evaluations coordinated by the new EMEA committee structure and the number of recommendations for product labelling on the safety Web-portal,

- Measuring the concordance between the recommendations for product labelling on the safety Web-portal and a sample of EU product information (after a period of 5-years has elapsed)

The overall objectives of the Community pharmaceutical legislation are to ensure proper functioning of the internal market for medicinal products and to better protect health of the EU citizens. These high level overall objectives are amenable to evaluation through an external study with the public health burden reduction having major scope for study by academic and clinical units (see the Annex 2 which refers to the existing extensive literature on public health burden of ADRs). Given that the two EU legal acts that are being modified contain existing general review clauses (Commission report on the operation of the procedures every 10-years) which will apply to the new provisions, any *ex-post* evaluation should therefore include these general reviews and any external study should be conducted in this context (to ensure best use of resources).

8. ACCOMPANYING DOCUMENTS

- Executive Summary of the Impact Assessment Report
- Annex 1: Summary of public consultations.
- Annex 2:Quantification of major economic impacts.
- Annex 3:Evolution of the Specific Policy Options