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COMMISSION STAFF WORKING DOCUMENT

IMPACT ASSESSMENT

Accompanying document to the

Proposal for a Regulation of the European Parliament and of the Council on the fees payable to the European Medicines Agency (EMA) for the conduct of pharmacovigilance activities in respect of medicinal products for human use

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Summary of the report

A. Need for action

Why? What is the problem being addressed?

The 2010 EU legislation on pharmacovigilance[1] has become applicable in July 2012. It streamlines the post-authorisation assessment and safety monitoring of medicines ('pharmacovigilance') for human use in the EU and significantly widens the tasks of the European Medicines Agency (EMA) with regard to pharmacovigilance, for both nationally and centrally authorised medicinal products, i.e. more than 350.000 products. These new tasks entail new costs for the EMA that need to be financed. The 2010 Pharmacovigilance legislation provides for fees to be charged by the EMA to marketing authorisation holders (MAH) to finance those pharmacovigilance activities carried out at EU level. The introduction of such fees requires legislative action which is the subject of this impact assessment.

What is this initiative expected to achieve?

The general objective is to define the structure and the level of the fees to be charged to MAH for pharmacovigilance activities performed at the EU level so that EMA can cover its costs including the remuneration of rapporteurs from Member States (MS) for their assessment work.

The specific objectives are:

- to ensure an adequate funding for pharmacovigilance activities at EU level,
- to establish a transparent, activity-based and cost-based fee system for the pharmacovigilance activities which are carried out at EU level,
- to define the structure of pharmacovigilance fees to reflect the principles of the 2010 Pharmacovigilance legislation.

What is the value added of action at the EU level?

The EMA is a decentralised agency of the European Union established by Regulation (EC) No 726/2004 and hence the decision on its funding and charging of fees can only be taken at the level of the EU. Therefore, only the Union can act to enable EMA to charge fees for pharmacovigilance.

B. Solutions

What legislative and non-legislative policy options have been considered? Is there a preferred choice or not? Why? Maximum 14 lines

New fees can only be introduced via legislative action, hence non-legislative policy options have not been considered. Legislative policy options that have been considered are:

Option 1 (baseline) – no change to the current situation (no introduction of fees for pharmacovigilance)

Option 2 - an annual flat fee charged to all authorised products in the EU

Option 3 - a combination of separate fees for procedure-based activities (charged to products subject to a

[1] Regulation (EU) No 1235/2010 amending Regulation (EC) No 726/2004 and Directive 2010/84/EU amending Directive 2001/83/EC

specific procedure for pharmacovigilance) and an annual flat fee for all other activities (charged to authorised products in the EU)

Option 4 - procedure-based fees only.

The preferred choice that has been identified is **option 3**, because a combination of procedure-based fees and an annual flat fee has been considered to be the most transparent, cost-based, activity-based and proportionate way of setting the new fees, in order to cover the costs of the pharmacovigilance activities at EU level. In this way, the products being part of a pharmacovigilance procedure at EU level will contribute to the financing of the cost of that procedure. At the same time, the costs of general pharmacovigilance activities of the EMA, and only that part of the cost, would be covered through an annual flat fee charged for authorised products in the EU which benefit from the EU pharmacovigilance system.

Who supports which option?

The EMA favours option 2, an annual flat fee. The position of industry is not explicit in terms of one single position on the matter. For example, the European organisation representing the pharmaceutical originator industry has expressed a preference for an annual flat fee, whereas the European organisation representing the generic industry is not in favour of that option.

The main interest of the national competent authorities of the MS is to ensure remuneration for rapporteurs providing scientific assessment within the Union-wide pharmacovigilance procedures. This is the case of all options involving policy action.

C. Impacts of the preferred option

What are the benefits of the preferred option (if any, otherwise main ones)?

Only the MAHs whose products are involved in EU pharmacovigilance procedures would pay for these procedures. As to the annual flat fee component, the estimated cost of specific pharmacovigilance procedures will not be included.

The rapporteurs from MS would receive remuneration for their services according to a fixed scale, based on the average workload and costs per type of procedure.

The annual flat fee would be lower than in option 2, only covering non-procedure-related costs. Such a structure of the fees would thus be perceived by stakeholders as the most transparent and proportionate option and the fairest fee model in the context created by the 2010 legislation on pharmacovigilance. This option would also take into account the requests of the Court of Auditors and the European Parliament for a cost-based remuneration of MS rapporteurs.

What are the costs of the preferred option (if any, otherwise main ones)?

Irrespective of the option chosen, the overall cost of the new 2010 pharmacovigilance legislation is estimated at € 38.5 m (€ 28 m for the EMA and € 10.5 m for rapporteurs from the MS).

How will businesses, SMEs and micro-enterprises be affected?

Under the preferred option, the effect on businesses would be the most proportionate, as they would pay for procedures only if and when they are involved in a procedure (procedure-based fees). The annual flat fee, affecting potentially all businesses, would only cover the cost of general pharmacovigilance activities of EMA. All

fees would be set to cover the respective estimated costs.

Small and medium-sized companies would pay 60% of the fees and micro-enterprises would be excluded from the payment of fees.

20% reduction of the annual flat fee would be granted to authorised generics, homeopathic, herbal and well-established use products, as these products are expected do have a well-established safety profile and should thus not be subject to the full fees.

Will there be significant impacts on national budgets and administrations?

As work is shifted from national to EU level with the new pharmacovigilance legislation, it is reasonable to expect that national fees would be readjusted if necessary, in order to reflect this change.

Will there be other significant impacts?

The number of authorisations would be taken into account in the charging of the procedure-based fee and the annual flat fee. However, the impact is difficult to foresee as it will depend on a number of factors, such as the type of products in the portfolio and the number of authorisations.

D. Follow up

When will the policy be reviewed?

The effect of the introduction of fees for pharmacovigilance would need to be monitored by the Commission based on information provided by the EMA. The European Commission may adjust, if necessary, the amounts of the fees.

1. INTRODUCTION

All medicinal products for human use have to be authorised either at Member State or EU level before they can be placed on the EU market. A strict testing and assessment of their quality, safety and efficacy is required before such authorisation is issued. In addition, once a medicinal product has been authorised and placed on the market in the EU, it continues to be monitored throughout its entire lifespan in order to ensure that any aspect which could impact the safety profile of such medicine is detected and assessed and that necessary measures, possibly including the withdrawal from the market, are taken. This process and science of monitoring the safety of medicines and taking action to reduce the risks and increase the benefits of medicines is called pharmacovigilance.

The EU pharmacovigilance system is one of the most advanced and comprehensive systems in the world and represents a robust and transparent instrument to ensure a high level of public health protection throughout the Union. The legal framework of pharmacovigilance for medicines marketed within the EU is provided for in Regulation (EC) No 726/2004 (the Regulation)[2] and in Directive 2001/83/EC (the Directive)[3]. The EU pharmacovigilance legislation has been subject to a major review and a comprehensive impact assessment that lead to the adoption of a revised legislation in 2010[4] (the 2010 Pharmacovigilance legislation), which strengthens and rationalises the system for monitoring the safety of medicines on the European market. This legislation provides for a number of EU-wide procedures to assess pharmacovigilance data which may lead to regulatory action. Some additional amendments were made to the pharmacovigilance legislation in 2012 following the Mediator-case[5].

The 2010 pharmacovigilance legislation streamlines the EU-wide post-authorisation assessment and monitoring of medicines and significantly widens the tasks of the European Medicines Agency (EMA) with regard to pharmacovigilance, irrespective of how the medicinal products have been authorised. Therefore, the EMA has pharmacovigilance competences for both nationally and centrally authorised medicines. To finance these activities, the 2010 Pharmacovigilance legislation provides for fees to be charged to marketing authorisation holders (MAH). These fees would not cover the pharmacovigilance activities of the National competent authorities (NCA) at national level whilst remuneration of the rapporteurs for scientific evaluations within the framework of the EU procedures would be included in the proposed fees. MS may therefore continue to charge fees for pharmacovigilance activities at national level.

Since the 2010 Pharmacovigilance legislation only concerns medicinal products for human use, the current proposal on pharmacovigilance fees can only concern medicinal products for human use.

This impact assessment report evaluates the various options for charging the fees to MAHs for the pharmacovigilance activities carried out by the EMA. It does not evaluate the

[2] OJ L 136, 30.4.2004, p. 1)

3 OJ L 348 on 31 December 2010

[4] Regulation (EU) No 1235/2010 amending Regulation (EC) No 726/2004 and Directive 2010/84/EU amending Directive 2001/83/EC

[5] Regulation (EU) No 1027/2012 amending Regulation (EC) No 726/2004 [OJ L 316/38, 14.11.2012] and Directive 2012/26/EU amending Directive 2001/83/EC [OJ L 229/1, 27.10.2012].

pharmacovigilance legislation as such, as this evaluation took place during the impact assessment of the legal proposal which lead to the adoption of the 2010 pharmacovigilance legislation.

2. PROCEDURAL ISSUES AND CONSULTATION OF INTERESTED PARTIES

As part of the preparation of a legal proposal on pharmacovigilance fees, DG SANCO in close collaboration with the EMA drafted a concept paper[6] for public consultation. Given that the pharmacovigilance procedures foreseen in the 2010 pharmacovigilance legislation are new procedures, the concept paper used existing procedures that were considered sufficiently similar as benchmarks for the new procedures. In addition, a pharmacovigilance service fee to be charged on an annual basis was considered in the paper in order to cover those activities of EMA that benefit industry in general, but for which it is not possible (or at least very difficult) to identify individual addressee(s).

Public Consultation

The Commission launched the public consultation on 18 June 2012 with a deadline for replies on 15 September 2012. In total, 85 replies were received (mainly from industry, but also from the Member States and other stakeholders). The summary of the replies to the public consultation is attached as Annex 2 and was also published on the DG SANCO website on 29 November 2012[7]. In general, the comments were overall negative notably as regards the amounts proposed. They were considered to be too high and without sufficient justification and transparency as regards the workload and costs. Grouping of MAHs, especially for submitting a single periodic safety update report (PSUR), was considered by many as not applicable in practice[8]. Many respondents questioned the benchmarks that were used and considered that pharmacovigilance fees should rather be based on the time spent and the associated costs for the work. Several industry respondents flagged the risk of possible duplicative charging of EMA and the Member States, given that many of the competent authorities in the Member States currently charge fees for pharmacovigilance. Particular concerns were expressed by SMEs, stating that despite the proposed fee reductions in the concept paper, the amounts were still too high. Also many responses from industry associations, representing the generics, homeopathics, herbals, and products authorised on grounds of well-established use, considered that the proposed fees would unfairly affect MAHs with a large portfolio of products with well-established safety profiles.

As a result of these comments, tis impact assessment was based on an evaluation of the workload and costs involved. The options (i.e. the structure and the level of the fees) in this impact assessment have been assessed accordingly.

[6] http://ec.europa.eu/health/files/pharmacovigilance/2012-06_concept_paper_en.pdf
[7] http://ec.europa.eu/health/human-use/pharmacovigilance/developments/2012-11_phv_fees_en.htm
[8] See also a special section on grouping in Annex 4.

Impact Assessment Steering Group

An Impact Assessment Steering Group has met five times on 20 January 2012, 13 March 2012, 11 May 2012, 19 November 2012 and 1 March 2013. The DGs invited to the meetings were SG, DG BUDG, DG ENTR, DG RTD, DG COMP, DG TRADE, DG ECFIN and LS. The EMA participated at these meetings, as well as in a number of other bilateral meetings with DG SANCO, in order to prepare this impact assessment.

3. PROBLEM DEFINITION

3.1. Context

All medicinal products in the EU are subject to a strict testing and assessment of their quality, efficacy and safety before being authorised. Once placed on the market they continue to be monitored so that any aspect which could impact the safety profile of a medicine is detected and assessed and that necessary measures are taken. This monitoring is called pharmacovigilance.

Pharmacovigilance is the process and science of monitoring the safety of medicines and taking action to reduce the risks and increase the benefits of medicines. In general, the pharmacovigilance activities include:

- Collecting and managing data on the safety of medicines
- Looking at the data to detect 'signals' (any new or changing safety issue)
- Evaluating the data and making decisions with regard to safety issues
- Pro-active risk management to minimize any potential risk associated with the use of the medicine
- Acting to protect public health (including regulatory action)
- Communicating with and informing stakeholders and the public
- Audit, both of the outcomes of action taken and of the key processes involved.

Stakeholders directly involved in pharmacovigilance include:

- Patients who are the users of medicines
- Doctors, pharmacists, nurses and all other health care professionals working with medicines
- Regulatory authorities, including the EMA and those in the Member States responsible for monitoring the safety of medicines
- Pharmaceutical companies and companies importing or distributing medicines.

Further description of Union-wide pharmacovigilance activities is provided in Annexes 3 and 4.

The revision of the Pharmacovigilance legislation

A major revision of the EU legislation on pharmacovigilance was introduced in 2010 through the adoption of (a) Regulation (EU) No 1235/2010 of the European Parliament and of the Council amending, as regards pharmacovigilance of medicinal products for human use,

Regulation No 726/2004 and (b) Directive 2010/84/EU of the European Parliament and of the Council amending, as regards pharmacovigilance, Directive 2001/83/EC.

The main pillars of the new 2010 pharmacovigilance legislation are proactive and proportionate risk management, higher quality of safety data, stronger link between safety assessments and regulatory action, strengthened transparency, communication and patient involvement, clear tasks and responsibilities for all parties (marketing authorisation holders, competent authorities, EMA), improved EU decision-making procedures (harmonised decisions and efficient use of resources) and the establishment of a new scientific committee at the EMA - the Pharmacovigilance Risk Assessment Committee (PRAC).

The new legislation became applicable in July 2012. The changes affect CAPs and non-CAPs. Given that the 2010 pharmacovigilance legislation provides a greater role for EMA in the area of pharmacovigilance in general, i.e. irrespective of how the medicinal products have been authorised (therefore including both nationally and centrally authorised products), EMA will for the first time be able to charge fees also for nationally authorised products.

Some additional amendments to the pharmacovigilance legislation were adopted in 2012. As a result of these amendments, it will be possible for a medicine to be withdrawn EU-wide if serious safety problems become apparent. A new automatic urgency procedure will include an EU safety evaluation if one Member State decides that, on the basis of pharmacovigilance activities, a medicine should be withdrawn from its own market. In addition, the list of products that are automatically subject to additional monitoring has been extended to include products that have the following post authorisation safety conditions: post authorisation safety studies, conditional or exceptional marketing authorisations.

Existing Fees and Financing of the EMA activities

The EMA budget for 2012 was €223,5 million of which €183 million stems from fees and €39 million from the EU budget.
Fees are currently charged by the EMA in accordance with Council Regulation (EC) No 297/95 on fees payable to the EMA for the Evaluation of Medicinal Products ('Fees Regulation')[9]. The Fees Regulation sets out fees for centrally authorised products (CAPs) including an annual fee (the full fee is currently € 95 900). For the application of the Fees Regulation, there are Implementing Rules adopted by the Management Board of the EMA[10]. According to those rules, the annual fee revenue may be used for the following activities for CAPs:

- 30% is meant to cover the EMA pharmacovigilance and inspection staff costs,
- 30% is meant to cover, *inter alia*, the rapporteur and co-rapporteurs work, where applicable, of scientific evaluation services provided at the request of EMA, e.g. annual product reports and specific reporting for pharmacovigilance and safety reports.

[9] OJ L 35, 15.2.1995 p.1
[10] Article 65 of Regulation (EC) No 726/2004 stipulates that the Management Board shall consist of one representative of each Member State, two representatives of the Commission and two representatives of the European Parliament. In addition, two representatives of patients' organisations, one representative of doctors' organisations and one representative of veterinarians' organisations shall be appointed by the Council in consultation with the European Parliament on the basis of a list drawn up by the Commission.

- 30% is meant to be attributed to special activities, to be determined by the EMA Management board, which also may have a link to pharmacovigilance for CAPs.

Whereas the previous (2004) wording of Article 67 of the Regulation provided that pharmacovigilance activities are to be publicly funded, the revised Regulation (as amended by the 2010 pharmacovigilance legislation) provides that industry is to be charged fees by EMA for the conduct of pharmacovigilance activities. In order to enable EMA to charge such fees, there is a need for a legal instrument.

The specific problems related to the absence of fees for pharmacovigilance activities are outlined in the following chapters.

3.2. Inexistence of financial instrument to implement the legislation and inadequate funding for pharmacovigilance activities at the level of the EU

Funding of EMA pharmacovigilance activities became inadequate due to the introduction of new tasks in the 2010 pharmacovigilance legislation. Prior to this legislation, the EMA was only tasked with pharmacovigilance of centrally authorised products. The new legislation has substantially increased the scope of EMA competence in pharmacovigilance, by including also products which are authorised via national procedures (i.e. mutual recognition, decentralised procedure, purely national procedures). The logic of EU-wide pharmacovigilance assessments per substance, regardless of the number of products corresponding to this substance (or the procedure under which they have been authorised) that are on the EU/EEA market, leads to a substantial workload associated with the corresponding Union-wide procedures and activities. Furthermore, the EU-wide assessments require designing, setting up, populating, maintaining and exploiting EU-wide databases of all authorisations (detailed description of the product and its authorised use) of medicinal products for human use in the EU/EEA, including all subsequent variations to those authorisations, adverse drug reactions declared for those products, as well as a repository for all individual periodic safety update reports drawn up for those products.

The legal instrument that would enable EMA to charge fees for the pharmacovigilance activities laid down in the 2010 pharmacovigilance legislation is missing. As a consequence, the existing fee structure of EMA does not reflect the requirements set out in the 2010 pharmacovigilance legislation and there is no adequate funding for pharmacovigilance activities at EU level. In particular, the EMA is not in a position to finance the full implementation of the new legislation. This has direct consequences as regards rapporteurs and co-rapporteurs from the national competent authorities in the MS, i.e. the absence of remuneration for their assessment work within the Union-wide procedures. This situation is unsustainable even in the short term.

3.3. Lack of transparency and clarity in current situation of pharmacovigilance fees across Europe

The existing fees for pharmacovigilance activities in the EU do not reflect the requirements and parameters set out in the 2010 pharmacovigilance legislation.

At the level of the EMA, as described above, there are no specific fees for the financing of the EMA's pharmacovigilance activities provided for in the 2010 pharmacovigilance legislation.

At the level of Member States and prior to application of the 2010 pharmacovigilance legislation, the pharmacovigilance activities of non-centrally authorised products was carried out by the individual national agencies, such as assessments of periodic safety update reports for products authorised in the MS. The financing of these activities follow different models decided at national level, e.g. through specific pharmacovigilance fees (e.g. fee for periodic safety update reports), generic (annual) fees, possible inclusion in authorisations fees, possible financing through national budgets, etc. Table 1 provides an indicative overview of national fee structures[12]. There were no EU-wide assessment procedures with the exception of pharmacovigilance (safety) referrals, though under a different legal framework. Under the new pharmacovigilance legislation, automatically triggered pharmacovigilance referrals are expected to lead to a substantial assessment workload.

The Commission's proposal for the 2010 pharmacovigilance legislation, was accompanied by a Financial Statement[11] according to which all costs related to activities resulting from the legislative proposal are to be covered through fees. Many NCAs currently charge the MAHs for pharmacovigilance activities, and hence there is also a need to ensure that MAHs are not charged twice for the same work. The 2010 legislation provides for pharmacovigilance assessments (i.e. pharmacovigilance referrals, PSUR assessments, PASS assessments) to be performed at EU level. Therefore, national fees should not cover those assessments. The non-procedure-related pharmacovigilance activities of the EMA under the 2010 pharmacovigilance legislation which also benefit the network, e.g. those relating to the EU database on adverse drug reactions, should only be charged for at the level of the EMA.

However, NCAs may still include in their national fees the costs for their own activity related to pharmacovigilance, e.g. collecting and transmitting to the EMA pharmacovigilance information. In addition, the NCAs will continue to carry out some pharmacovigilance activities for NAPs, such as signal detection (which EMA is doing for CAPs) as well as the assessment of those PASS which are conducted only in one MS (as PASS which are conducted in more than one MS will be subject to the EU-wide procedures and thus covered by the fees charged by EMA). As the EU-wide activities which are to be covered by the proposed pharmacovigilance fees will be defined, it is reasonable to expect that NCAs will not include in their national fees pharmacovigilance activities that are not (or no longer) performed at national level.

The various national fee structures may be adapted, if needed, to the new 2010 pharmacovigilance legislation only when the fees for pharmacovigilance levied by the EMA are actually introduced.

It would be necessary for the NCAs to ensure that there is no double charging at national level of the activities for which a fee is charged by the EMA. To this end, any proposed fees of EMA should be transparent and well defined in order for MAHs and MS to be able to identify which pharmacovigilance activities these fees would cover.

[11] http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=COM:2008:0664:FIN:en:PDF.

Table 1: Pharmacovigilance fees charged by some NCA[12]

	PSUR fee National procedure	PSUR fee MRP / DCP		Annual Fee
		CMS	RMS	
Austria	500 €	500 €	3.600 €	
Belgium	1.211 €	1.211 €	2.422 €	
Bulgaria				489 €
Czech Republic	in Annual Fee			762 €
Denmark	871 €	871 €	1.742 €	1.180 €
Estonia	in Annual Fee		320 €	160 €
Finland	in Annual Fee			1.200 €
Germany	1.300 €	1.300 €	4.400 €	
Ireland	in Annual Fee			812 €
Italy				1.000 €
Latvia	1.423 €			500 €
Lithuania	273 €	178 €	1.143 €	
Malta			2.300 €	
Netherlands	in Annual Fee			1.050 €
Slovenia	1.500 €	250 €	11.750 €	
Spain	375 €	375 €		118 €
Sweden	in Annual Fee			5.366 €
UK	in Annual Fee			28.520 €

Source: Web pages of NCAs in MS

3.4. Baseline scenario – how will the situation evolve if fees for Union-wide pharmacovigilance activities are not introduced

With an unchanged policy and thus no financial instrument in place for the implementation the revised pharmacovigilance legislation, there would be a growing number of pharmacovigilance procedures under the 2010 pharmacovigilance legislation for which there would be no funding available. This already leads to difficulties in finding rapporteurs and co-rapporteurs, as the system has to operate currently on a non-remunerated basis. Moreover, apart from pharmacovigilance, there are already some activities involving NCAs and the EMA which are non-remunerated. The pharmacovigilance procedures which represent a considerable workload (e.g. an average of 600 PSUR assessments expected per year) would add further constraints to the system.

In the absence of a change to the current situation, the future would be even less transparent, as the new legislation covers both CAPs and non-CAPs.

As mentioned above, the MAHs holding CAPs pay currently an annual fee to EMA for each MA[13]. The annual fee revenue of EMA and the actual contribution of this revenue to

[12] Table 1 presents a non-exhaustive and indicative view of the level of fees levied at the level of Member States. Despite the fact that data is not available from all NCAs, available data suggests that there are significant differences in the structure and level of national fees for pharmacovigilance.

[13] Article 3 paragraph 6 of the Fees Regulation

pharmacovigilance activities for CAPs as set out in the Implementing Rules of the Fees Regulation[14] is being examined in detail based on information from the EMA. On the basis of this work, an adjustment with regards to the annual fee revenue may be necessary.

Further projection of the baseline scenario is provided in section 6.1.

3.5. Subsidiarity analysis and right to act at EU level

The EMA is a decentralised Agency of the EU under the Regulation and hence the decision on its funding and charging are to be taken at the European level. The new pharmacovigilance legislation provides a legal base for EMA to charge fees for pharmacovigilance. Only the Union can act to introduce these fees for pharmacovigilance. As mentioned above, the proposed legislation will only deal with fees for EMA (and not fees charged by NCAs for which the EU is not competent).

As to the legal instrument to be used, it should be noted that the current Fees Regulation is a Council Regulation, that was last amended in 2005. Since the Treaty on the Functioning of the European Union became applicable, all legislative procedures are normally based on the ordinary legislative procedure (previously 'co-decision procedure') involving both the Council and the European Parliament. For legal certainty, it is proposed to create for EU pharmacovigilance fees a separate legal instrument, i.e. a Regulation of the European Parliament and of the Council, which will be subject to the ordinary legislative procedure (Article 294 of the TFEU).

4. OBJECTIVES

The general objective which this initiative aims to contribute to, is to ensure a high level of human health protection in the EU as well as to promote the functioning of the internal market.

The specific objective is to ensure the implementation of the 2010 pharmacovigilance legislation through defining the structure and the level of the fees charged by the EMA to MAHs for Union-wide pharmacovigilance activities. In order to make sure that adequate funding for those pharmacovigilance activities is available, such a fee structure/level should allow for the EMA to cover the estimated costs, including remuneration of rapporteurs from the NCAs for the assessment they provide. It should also underpin the establishment of a transparent, activity based and cost-based fee system of the EMA for pharmacovigilance activities at EU level.

The operational objectives and the criteria for assessing the alternative fee systems stem directly from the specific objectives of the initiative, i.e. to establish the appropriate structure and the level of fees for pharmacovigilance activities. They are as follows:

1. Transparency – i.e. clear relationship between the type and level of fee and the corresponding work carried out. Fees in general should reflect the overall average level of work required and should cover all the administrative, technical and scientific activities provided in a transparent manner. The link between services provided and fee charged should be clear.

[14] The amount (or, in some cases, the range) of the existing fees are laid down in the current Fees Regulation, whereas the Implementing rules specify more precise amounts, exemptions and allocation of the fee revenue.

2. Fairness - i.e. the notion that the MAH should contribute to the financing of pharmacovigilance activities on the basis of potential safety concerns, recognising that not all products have the same safety profiles. Such an approach is also in line with the underlying pharmacovigilance legislation, e.g. where the frequency of PSUR submission is to be established on the basis of the safety profile (expected risks) of each concerned substance. The fee should therefore be constructed in a way aimed at ensuring a balance between the amount paid, the work carried out and the potential risks. Another dimension of the fairness principle is to avoid cross-subsidisation and double charging as far as reasonably achievable.
3. Stability - i.e. the need to provide for a stable pharmacovigilance fee system at EU level based on the highest possible degree of financial predictability and avoiding variable remuneration of similar scientific services. However, given that the 2010 pharmacovigilance legislation provides for EU-wide procedures which cannot be predicted with 100% certainty, a degree of uncertainty in respect of fee revenue and costs will remain.
4. Simplicity – i.e. minimum additional administrative complexity and burden. This criterion is linked to the importance that the EU pharmacovigilance fee system be well accepted by stakeholders. A genuinely simple system is, however, difficult to achieve, given the complexity of the underlying legislation and the fact the EMA will, for the first time, charge MAHs holding non-centrally authorised products.

5. OPTIONS

Several policy options to collect pharmacovigilance fees were considered. Fee reductions or waivers foreseen and proposed (e.g. for SMEs, micro-enterprises) are part of the individual options. The calculation of the amount of the fees for each option based on the estimated costs of the conducted pharmacovigilance activities is outlined in Annex 4.

The SMEs reductions projected in the individual options are based on the comparisons of the added value per employee as a possible measure of profitability of companies. Using this measure, small and medium enterprises in the pharmaceutical sector are on average 40 % less profitable than non-SMEs and accordingly it is proposed that these enterprises will pay 60 % of the standard fee. The micro-enterprises are assumed to be entirely exempted from the obligation to pay parmacovigilance fees since the already small number of authorisations held by SMEs is further decreased in case of micro enterprises which implies that the administration burden to collect the fee would offset the benefits from its collection. Exempting micro-enterprises would thus not impair the objectives of the initiative. SME aspects and further justifications of the fee discounts is discussed in Annex 5.

Option 1: No change to the current situation

The first option would be to keep the current situation unchanged. No specific pharmacovigilance related fees to be charged by EMA would be introduced.

Option 2: One flat fee covering all pharmacovigilance activities

A flat fee for pharmacovigilance activities of EMA would be introduced and applicable annually to all MAHs having at least one medicinal product authorised in the EU. The fee amount charged to each particular MAH would be calculated on the basis of chargeable units corresponding either to individual entries in the EU database set by article 57(2) of Regulation 726/2004 with respect to medicinal products ('EV-codes') related to that particular MAH, or to marketing authorisations defined at national level or to the MAH itself. The fee per chargeable unit would be € 122 in case the EV-code is chosen as such. The overall amount of fees collected would on average cover the estimated cost of all Union-wide pharmacovigilance activities carried out in one year.

Reductions (fee incentives) for certain categories of MAHs, such as SMEs would apply. A decreased flat fee for medicinal products for which the MAH is a SME would be set at the level of 60 % of a full flat fee. No fee would be charged for medicinal products for which the MAH is a micro-enterprise.

A fee reduction of 20% is proposed for authorised generics, homeopathic, herbals and medicinal products authorised on grounds of well-established use[15]. A large portfolio of these products with a long history of use usually implies that their safety profile is well known and, consequently, they are less likely to be subject to EU pharmacovigilance procedures. With some exceptions, these are the categories of products which are normally not required to submit PSURs under the 2010 pharmacovigilance legislation and this approach is also consistent with the views expressed in the public consultation. Finally, it should be noted that some CAPs such as generics are currently subject to a reduced annual fee under the Fees Regulation.

Option 3: A combination of separate fees for procedure-based activities and an annual flat fee for all other activities

Two separate categories of fees would be charged. (1) Different fees for specific pharmacovigilance activities/procedures, i.e. for the assessment of PSURs, the assessment of the PASSs and assessment in case of pharmacovigilance referrals would be charged to all MAHs having a medicinal product that is subject to the procedure in question. Additionally, (2) an annual flat fee would be charged to all MAHs having at least one medicinal product authorised in the EU. This additional fee would cover only the costs of the activities of EMA other that those related to the specific procedures.
The overall amount of fees collected would cover on average the estimated cost of all Union-wide pharmacovigilance activities.

A fixed overall fee amount per PSUR assessment procedure would be based on its estimated average cost of € 19 484. The division of the fee among the MAHs would be based on the proportion of chargeable units (e.g. EV-codes) related to each MAH whose product is subject to the procedure compared to all other MAHs involved in the procedure.

A fixed overall fee amount per PASS assessment would be based on its estimated average cost of € 42 962. In the case of joint studies, this amount will be divided by the number of

[15] Products which have been registered at national level under the procedure laid down in Chapters 2 and 2a of Directive 2001/83/EC are excluded from the fee.

marketing authorisation holders that have submitted the joint study in order to constitute the individual amount payable by this entity (i.e. the MAH).

A fixed overall fee amount per pharmacovigilance referral will be based on its estimated average cost of € 168 542. As with the PSUR assessment, the division of the fee among the MAHs would be based on the proportion of chargeable units related to each MAHs having products that are involved in the procedure.

The annual flat fee for the pharmacovigilance activities not directly related to any of the three procedures above would be based on the estimated cost of those activities and charged annually to all MAHs having medicinal products authorised in the EU, with some exceptions explained below. The total amount charged to a particular MAH would be calculated on the basis of chargeable units related to that particular MAH. Should the EV-code be used, the amount would be € 60.

Given that the new pharmacovigilance activities to be carried out at the EU level relate to both CAPs and non-CAPs for the benefit of all marketing authorisation holders in the EU, the holders of medicinal products authorised in the EU should contribute to the financing of these activities. It is proposed that MAHs of CAPs be exempted from the payment of the envisaged annual flat-fee component of the pharmacovigilance fees, as they already pay to EMA the annual fee applicable to CAPs under the existing Fees Regulation.

Reductions (fee incentives) for SMEs would apply both to the annual flat fee and to the procedure-based fees. MAHs that are SME would be charged 60 % of the applicable full fee and no fee would be charged for medicinal products for which the MAH is a micro-enterprise.

In respect of the flat fee component, a fee reduction of 20% is proposed for authorised generic, homeopathic, herbal medicinal products and medicinal products authorised on grounds of well-established medical use, for the same reasons as outlined for the flat fee in option 2[16]. However, where such products are involved in the EU pharmacovigilance procedures, there would be no fee reduction and the normal procedure-based fee would apply.

Option 4: Procedure based fees only, no flat fee

All costs for pharmacovigilance activities in a given year would be covered on average through fees charged only to those MAHs having, in that particular year, a medicinal product involved in one of the procedures, i.e. (1) the assessment of PSURs, (2) the assessment of PASSs and (3) the assessment in case of pharmacovigilance referrals. The non-procedure related costs of the EMA would be proportionally distributed among these three procedures, based on the workload involved within the procedures.

A fixed overall fee amount per single PSUR procedure would be based on its estimated average cost including the proportion of non-procedure related costs, totalling to € 33 794. The distribution of the fee among the MAHs would be based on the proportion of chargeable units (e.g. EV-codes) related to the MAHs for each active substance (or combination of substances) that is subject to the PSUR procedure.

[16] Products which have been registered at national level under the procedure laid down in Chapters 2 and 2a of Directive 2001/83/EC are excluded from all fees.

A fixed overall fee amount per single PASS assessment would be based on its estimated costs including the proportion of non-procedure related costs, totalling to € 84 966. In the case of joint studies, this amount will be divided by the number of marketing authorisation holders that have conducted the study.

A fixed overall fee amount per pharmacovigilance referral would be based on its estimated costs including the proportion of non-procedure related costs, totalling to € 332 136. The distribution of the fee among the MAHs would be based on the number of MAHs taking into account the number of EV-codes they hold in relation to the product(s) in question.

Reductions (fee incentives) for certain categories of MAHs, such as SMEs, would apply. A SME fee would be set at the level of 60 % of a full fee per procedure and no fee would be charged to the MAH which is a micro-enterprise. No other fee reductions or fee waivers are foreseen for marketing authorisation holders under this option.

6. ASSESSMENT OF IMPACT OF THE OPTIONS

The impact of each option is considered for three main stakeholders who will be directly influenced, i.e. (1) the MAHs, (2) the National competent authorities (NCAs) of the MS (3) and the EMA and the European Commission.

As indicated in chapter 4, the criteria for assessing the alternative fee systems stem directly from the operational objectives of the initiative, i.e. to establish the appropriate structure and the level of fees for pharmacovigilance. The criteria are defined as follows:

Transparency – i.e. clear relationship between the type and level of fee and the corresponding work carried out.

Fairness - i.e. the notion that the MAH should contribute to the financing of pharmacovigilance activities on the basis of potential safety concerns, recognising that not all products have the same safety profiles. Avoiding cross-subsidisation and double charging as far as reasonably achievable is another dimension of the fairness principle.

Stability - i.e. the need to provide for a stable pharmacovigilance fee-system based on the highest possible degree of financial predictability and avoiding variable remuneration of similar scientific services.

Simplicity – i.e. minimum additional administrative burden and complexity.

As regards Member States and their scientific involvement as rapporteurs / co-rapporteurs, these activities would be covered through remuneration received from the EMA for each assessment procedure in which the rapporteurs of NCAs would participate. The level of remuneration will be based on the average costs per type of procedure as estimated in Annex 3. As in all options, the exact yearly amount that will be paid in remuneration of rapporteurs from the MS cannot be predicted with a 100 % accuracy, given that the exact number of procedures is unknown. It is however assumed that the total amount of € 10.5m intended to be collected from MAHs[17] would be paid overall to MS in an average year.

Since a cost-based approach has been chosen, options 2 to 4 should on average ensure adequate funding of EMA's pharmacovigilance activities. Option 1, according to which no legal proposal on pharmacovigilance fees would be adopted, would obviously not ensure this.

Annex 4 outlines the calculations of the amount of the fees for each considered option. The calculations are based on the estimated costs of the pharmacovigilance activities presented in Annex 3. The results of the calculations as well as the main arguments in favour and against each option are outlined and analysed under sections 6.1 – 6.4 below.

Further information on impacts according to the criteria is summarised in Annex 7.

[17] See Annex 3

6.1. Option 1: No change to the current situation

In general, a potential lack of action would prevent the 2010 pharmacovigilance legislation from being fully implemented and would therefore totally undermine the public health benefits deriving from the legislation, as analysed in the corresponding impact assessment of 2008. The 2010 legislation explicitly foresees the introduction of fees for pharmacovigilance (see Annex 6).

Impacts on marketing authorisation holders (MAH)

The marketing authorisation holders would not benefit from the enhanced and rationalised pharmacovigilance system introduced by the 2010 pharmacovigilance legislation. Moreover, MAHs would lack clarity as regards the sustainability and the funding of pharmacovigilance activities in the EU.

Impacts on Member States

As a consequence of the EMA not receiving adequate funding for the implementation of the pharmacovigilance activities as assigned to it by the 2010 pharmacovigilance legislation, the Member States' rapporteurs and co-rapporteurs would, in turn, not be remunerated by the EMA to cover their costs for their assessment work within the EU procedures. This would in turn reinforce the negative impact on the EMA, as it would become increasingly difficult to find rapporteurs for the individual procedures.

Impacts on the EMA and European Commission

In this scenario, the EMA would not be in a position to fully implement its new tasks with regard to the 2010 pharmacovigilance legislation that has put the EMA at the centre of the new pharmacovigilance system in the EU. This would be due to the absence of adequate funding for the costs incurred for the performance of these tasks.

In such an event, the Commission's position would be perceived as a failure to act in view of its exclusive powers to put forward legislative proposals within the EU legislative framework. As mentioned above, the 2010 pharmacovigilance legislation foresees the introduction of fees. This would therefore also be perceived as a loss of credibility of the Commission. The financial statement that accompanied the legal proposal in 2008 foresaw that all costs relating to pharmacovigilance should be covered through fees. Moreover, the public health benefits envisaged as a consequence of the pharmacovigilance legislation would not be achieved.

6.2. Option 2: One annual flat fee covering all pharmacovigilance activities at EU level

Impacts on marketing authorisation holders (MAH)

In this scenario, each MAH, with the exceptions explained in Chapter 5, would be charged once per year for all pharmacovigilance activities performed at EU level, based on an 'insurance' principle, rather than on an 'incident' principle. All products on the market would

be considered as potentially subject to safety concerns at the same level and would contribute equally to the financing of the pharmacovigilance activities at EU level. Such a system would not be perceived as fair by all MAHs, especially those whose products have a well-established safety profile and would thus normally be less involved in the EU procedures. Moreover, the level of the fee would be perceived differently by the MAHs depending on whether they have had dealings with the EMA. The perception of the fee level by MAHs would also depend on their market power and the size of their product portfolio.

A flat fee is a predictable fee that MAHs would be able to take account of in their financial planning. Also, MAHs would not be charged separately for any individual EU procedures, as all costs would have been covered through the flat fee. At the same time, flat fees are often considered less transparent compared to fees for well-defined, specific activities, where such a definition is possible. Thus, individual fees might be perceived by some industry stakeholders as non-cost-based. This is the case in particular for MAHs that do not expect any (or very little) involvement in the EU procedures.

Also, MAH that are unlikely to be concerned by any of the EU procedures and those that have at present no contacts with EMA are likely to question the fee, particularly if they already pay pharmacovigilance fees to one or several NCAs.

In comparison with options 3 and 4, option 2 is also less transparent and, therefore, the MAHs may perceive that they are charged twice for the same work by EMA and by NCAs.

Impacts on Member States

Rapporteurs and co-rapporteurs from MSs would cover their costs for their assessment work, through remuneration received from the EMA for each assessment procedure related to pharmacovigilance at EU level. As under any of the options 2-4, rapporteurs would be remunerated according to a scale based on average costs and workload per type of evaluation procedure. As in all options (save option 1), remuneration would take place whenever the rapporteur is carrying out work within any of the EU procedures.

Impacts on the EMA and the European Commission

In this scenario, the EMA would charge to all MAH a single pharmacovigilance fee, for all authorised products, in accordance with structured information on medicinal products stored in the database populated in the context of Article 57(1)(l) and Article 57(2) of the Pharmacovigilance Regulation *(Regulation (EU) No 1235/2010 of the European Parliament and of the Council of 15 December 2010).*

This means a stable, predictable revenue for the EMA. It is anticipated that the flat fee would be charged annually. The invoicing and collection of fees would be automated to the extent possible. This would alleviate the administrative work and the number of transactions and invoiced parties will be slightly lower than under option 3 but considerably higher compared with option 4.

In this scenario, the collection of the fee would be disconnected time-wise from the actual pharmacovigilance procedures. The EMA would therefore have to ensure sound financial management of the pharmacovigilance fee revenue throughout the year, including earmarking funds for remuneration of MS rapporteurs, with underlying uncertainties regarding the actual occurrence and the timing of some EU procedures, i.e. pharmacovigilance referrals and PASS assessments. Therefore, this option may lead to a risk of insufficient funding for EMA should the number of procedures, notably referrals, increase substantially beyond what is expected.

6.3. Option 3: A combination of separate fees for procedure based activities and an annual flat fee for all other activities at EU level

Impacts on marketing authorisation holders (MAH)

In this scenario, MAHs would be charged as follows:

- all MAHs in the EU[18] (with the exceptions explained in Chapter 5) would be charged an annual flat fee, as in option 2, but for a lower amount, depending on the number of products/authorisations in their portfolio;
- MAH having at least one product involved in a pharmacovigilance procedure would be charged the corresponding procedure-based fee.

The MAHs that are not involved in any EU procedure, would only pay the annual flat fee. As regards this fee fee, the same advantages and drawbacks apply as explained under option 2.

In terms of transparency, fairness and proportionality, the procedure based fee is the most service- / cost-oriented fee and scores better as compared to option 2. Despite the fact that the flat fee component is not fully cost-based on individual level, this option overall presents the most detailed fee grid, which would facilitate comparison with national fees. This option, therefore, would facilitate the adjustment by Member States, if necessary, of their national fees.

Some of the procedure-based fees (i.e. PhV referrals, PASS) would be less predictable for MAH compared to the flat fee because the actual occurrence and the scope of such procedures are not known in advance.

Impacts on Member States

As under the options 2 and 4, MS acting as rapporteurs would be remunerated according to a fixed scale based on average estimated costs per type of procedure. As for the other options, the exact yearly amounts that would be paid to the MS is not predictable given that the number of procedures are more difficult to predict (except for PSURs). However, remuneration is linked to the actual work carried out.

Under this option the fees are, therefore, proportionate to the workload and the costs, but cannot be entirely predictable by the inherent nature of the pharmacovigilance activities at EU level.

Impacts on the EMA and the European Commission

The fee revenue would overall cover the average costs of the EMA. The fee revenue is thus proportionate to its workload. For the annual flat fee, the same advantages and drawbacks apply as indicated under option 2 above. However, in comparison with option 2, the actual level of the annual flat fee would be considerably lower (as cost of procedures would not be included in the calculation of that fee). The administrative work for EMA would be higher compared to option 2. This is because contrary to the annual flat fee component, the invoicing of the procedure-based fee component cannot be fully automated. Moreover, the number of

[18] as per information registered by the EMA in the database set up by Art 57 of the Regulation

invoiced parties will be higher but this will largely depend on the number of EU procedures and the number of MAHs and products involved in the procedures.

This option would ensure the funding of the procedure-related activities in a timely manner.

The EMA would have to apply the fee reductions for authorised generics, homeopathic, herbal and medicinal products authorised under well-established use in respect of the annual flat fee component.

The additional number of invoiced parties may be estimated as follows:

- 3.275 additional invoiced parties for the procedure-based activities, i.e.:
  - for PSUR assessments: (approximately 600 per year), 1.800 additional invoiced parties with amounts itemized per MAH
  - for PASS assessments (approximately 35 per year), 35 additional invoiced parties (if several MAHs conduct the study jointly, they may share the fee amongst themselves)
  - for pharmacovigilance referrals (approximately 40 per year), 1.440 additional invoiced parties[19]

6.4. Option 4: Only procedure-based fees

Impacts on marketing authorisation holders (MAH)

In this option, the 'insurance' principle would be completely eliminated in favour of an approach that is entirely based on an 'incident' principle. Only MAHs whose product(s) is (are) concerned by a pharmacovigilance procedure would be charged a fee at the time when the procedure is launched. The fee levels per procedure would be higher than the procedural fee-levels in option 3 where procedure-based fees are combined with an annual flat fee.

The same advantages and drawbacks apply as explained under option 3 with respect to the procedural fee component, with the difference that under this option, the general EMA costs (i.e. those which are not linked to any procedures) would be distributed only amongst those MAHs that are included in the procedures. If there is a proportionate distribution of the non-procedure related costs in a transparent way this approach might be acceptable for the MAHs. On the other hand, those MAHs that are not subject to any EU procedures would not contribute to the financing of the system whilst indirectly and potentially (i.e. should they be subject to EU procedures in the future) benefiting from it. In this respect, option 4 is likely to be less transparent, and less fair and proportionate than option 3.

Impacts on Member States

As under options 2 and 3, MS would be remunerated according to a fixed scale based on average estimated costs for each type of procedure. However, the exact yearly amounts that would be paid to the MS are not predictable given that the number of procedures is more difficult to predict (except for PSURs). Remuneration is linked to the actual work carried out.

[19] The EMA's forecast is an average number of 36 MAHs involved in a pharmacovigilance referral

Impacts on the EMA and European Commission

As opposed to option 2 (a single pharmacovigilance fee) and option 3 (with respect to the flat fee component), the EMA would only charge a fee when an EU procedure is launched.

The same advantages and drawbacks apply as explained under option 3 with respect to the procedural fee component. As regards the administrative work, the main difference is that the number of transactions and invoiced parties is significantly lower compared to both options 2 and 3. Also, there is no need for EMA to apply any fee reductions for authorised generics, homeopathic, herbal and medicinal products authorised under well-established use (which they would do in respect of the flat-fee component under option 3). The regularity of PSUR assessments (as opposed to the other procedures which are less predictable) would have a positive effect on the funding of non-procedure related activities of EMA.

Under this option, the fees are proportionate to the workload and the costs, but cannot be predictable due to the inherent nature of the pharmacovigilance activities at EU level.

6.5. Comparison of the options

The criteria for evaluating the options follow the principles of effectiveness, efficiency and coherence. As already explained, the specific criteria against which the options are compared include (1) transparency of the fee levels and structure, (2) stability and financial predictability of fees, (3) the simplicity of the fee structure and (4) fairness and proportionality of fees.

Table 2 below summarises the analysis of individual options from chapters 6.1-6.4 and Annex 7 and assigns the scores of how well each option meets the criteria as compared to baseline scenario. The assessment of the way the different options meet the four criteria / objectives has been performed by attributing scores as per a scale from 1 to 3. Scores are relative compared to the baseline scenario and are defined as follows:

1 Slightly more positive effect as regards meeting the criterion / objective
2 More positive effect as regards meeting the criterion / objective
3 Very much more positive effect as regards meeting the criterion / objective

Table 2: Comparison of options and how they meet objectives relative to baseline

Options / Objectives	transparency	stability / predictability	simplicity	fairness / proportionality
1. Baseline	0	0	0	0
2. Flat Fee	1	3	3	1
3. Combination of an annual flat fee and procedure-based fees	3	2	1	3
4. Procedure-based fees only	2	1	2	2

Analytical hierarchy process technique was used in order to assign weights to each criterion to reflect and formalize its relative importance. The individual steps of that analysis are described in detail in Annex 9. The results suggest the following relative weights: 45 % on fairness and proportionality, 32 % on transparency, 14 % on stability and predictability and 9 % on simplicity. This hierarchy of relative importance of all four criteria was applied to the analysis of individual options summarised in Table 2 above. The result of this final step of the comparison between the options is outlined in Table 5. The final absolute scores determine the ranking of the options in terms of achieving objectives.

Table 5: Final comparison of options

Options / Objectives	transparency	stability / predictability	simplicity	fairness / proportionality	**Total Score**
Option 1	0	0	0	0	**0**
Option 2	3	4	3	5	**15**
Option 3	10	3	1	14	**27**
Option 4	6	1	2	9	**19**

Based on that analysis, option 3, i.e. the combination of procedure-based fees and an annual flat fee, is the preferred option.

A combination of procedure-based fees and an annual flat fee has been considered to be the most transparent, cost-based, activity-based and proportionate way of setting the new fees, in order to cover the EMA's costs. In this way, the medicinal products being part of a pharmacovigilance procedure at EU level will contribute to the financing of the cost of the procedure. At the same time, the costs of general pharmacovigilance activities of the EMA, and only that part of the cost, would be covered through an annual flat fee charged for all authorised products in the EU, which benefit from the EU pharmacovigilance system.

7. MONITORING AND EVALUATION

The monitoring will be linked to the implementation of annual budget of the EMA. The annual activity report on the performance of the EMA will provide reliable information and key indicators such as

• Number of EMA staff involved in pharmacovigilance activities as per the legislation applicable during the reference period.
• Number of hours outsourced to third parties with specification of the activities concerned.
• Overall pharmacovigilance costs and a breakdown of costs relating to each of the procedures referred to in Articles 4-6 of this Regulation as well as the costs relating to the activities referred to in Article 7 of this Regulation.
• Number of procedures relating to the single assessment of periodic safety update

reports, as well as number of marketing authorisation holders and number of chargeable units per procedure; number of reports submitted per procedure and number of marketing authorisation holders that have submitted a joint periodic safety study report.
• Number of procedures relating to the assessment of post-authorisation safety studies; number of marketing authorisation holders having carried out such studies and number of marketing authorisation holders that have submitted a joint study.
• Number of procedures relating to the referrals initiated on the basis of pharmacovigilance data as well as number of marketing authorisation holders and number of chargeable units involved per marketing authorisation holder and per procedure.
• Number of marketing authorisation holders that have claimed a small and medium-sized enterprise status involved in each procedure; number of marketing authorisation holders whose claim has been denied. • Number of marketing authorisation holders that have claimed a micro enterprise status; number of marketing authorisation holders whose claim for fee exemption has been denied.
• Number of marketing authorisation holders of medicinal products referred to in Article 10(1) of Article 10a of Directive 2001/83/EC that have benefitted from reduced annual flat fees; number of chargeable units per marketing authorisation holders concerned.
• Number of invoices sent out in respect of the annual flat fee and average and overall amount invoiced to marketing authorisation holders. • Number of marketing authorisation holders that have claimed a small and medium-sized enterprise or a micro enterprise status for each annual application of the annual flat fee; number of marketing authorisation holders whose claim has been denied.

These indicators will allow assessing the sustainability of EMA financial resources in the area of pharmacovigilance over a period of time. The overall effectiveness and efficiency of the pharmacovigilance services offered to industry by the EMA including work of rapporteur NCAs will be measured by the EMA using indicators such as timeliness and quantity of the services provided.

All this should be sufficient to ensure an effective monitoring of the functioning of the proposed action. On the basis of the data submitted by EMA, the Commission will consider whether there is a need to revise the level of the fees.

ANNEX 1 - LIST OF ABBREVIATIONS

ADR:	Adverse Drug Reaction
Article 57(2) database	A database based on the list of all medicinal products for human use authorised in the EU which is set up and maintained by the EMA in accordance with Article 57(1)(l) and Article 57(2) of Directive 2001/83/EC.
CAP:	Centrally Authorised Product
CMDh:	Coordination Group for Human Medicinal Products
CHMP:	Committee for Medicinal Products for Human Use
Chargeable unit	Unit used for the charging of the annual flat fee and for dividing the fees per procedure among MAHs.
EMA:	European Medicines Agency
EURD list	European Union Reference Data list (list of active substances/combination of substances with dates and frequency for submission to EMA of PSURs for substances that are authorised in more than one MS) The EURD list, which became applicable in April 2013, is intended to optimise the management of PSURs assessment within the EU while supporting transparency. It aims to provide predictability to the various stakeholders in terms of workload related to PSURs, taking into account the currently known safety profile of the active substances and combinations of active substances. The knowledge about the safety profile has been considered when determining the frequency of the submission of PSURs, i.e. for substances with well-known safety profiles that have been on the market for a longer period, PSURs will be required less frequently compared to newer substances.
EV:	EudraVigilance database (of ADRs)
EV-code:	An individual entry in the Article 57(2) database intended to describe with maximum precision a medicinal product in the EU, taking into account the different ways in the EU of assigning authorisation numbers to and counting medicinal products. The medicinal product is described as sold or supplied to a consumer or patient. This is a harmonised way of registering medicinal products authorised throughout the EU, according to methodology developed by the EMA, in accordance with ISO standards of product definition. EV code is the most harmonised common denominator used across the EU.
FTE:	Full Time Equivalent
MA:	Marketing Authorisation
MAH:	Marketing Authorisation Holder

MRP / DP:	Mutual Recognition Procedure / Decentralised Procedure
MS:	Member State
NAP:	Nationally Authorised Product (including MRP/DP)
NCA:	National Competent Authority
PASS:	Post-Authorisation Safety Study
PRAC:	Pharmacovigilance Risk Assessment Committee
PSUR:	Periodic Safety Update Report

ANNEX 2 – SUMMARY OF THE PUBLIC CONSULTATION

On 18 June 2012 the European Commission published a Concept Paper[20] on the introduction of fees to be charged by the European Medicines Agency for pharmacovigilance. The consultation period ended on 15 September 2012.

The Commission received 85 replies (9 requesting confidentiality):

- 66 from industry, associations and individual companies
    - including 30 from SMEs
- 12 from national competent authorities (NCA),
    - AT, DE, DK, EL, ES, IRL, MT, NL, NO, SE, and UK
    - HMA,
- 4 from civil societies and other associations,
- 3 from individual persons.

This document summarises the responses to the public consultation on the concept paper. It is in no way to be understood as an endorsement of any comment. For the sake of brevity, consultation items are not reproduced. Therefore, this summary should be read in conjunction with the consultation items set out in the concept paper.

The public consultation is part of the on-going impact assessment exercise. The information and views gathered in this public consultation will be taken into consideration in the impact assessment process.

GENERAL REMARKS

The public consultation was appreciated by stakeholders. However, the vast majority of respondents did not support or fully support the proposed fees, notably as regards the amounts proposed. There was generally a view that the concept paper did not present sufficient information about the basis for the estimations (in terms of workload and costs) of the proposed fees.

Many respondents question the benchmarks that have been used and consider as a more appropriate approach the time used and the associated costs for the work. The majority of the respondents consider the proposed fees as being too high and without sufficient justification and transparency.

The vast majority of the respondents made reference to the financial statement of 2008[21] questioning the significant increase in the proposed fee levels compared with this financial statement and the lack of sufficient explanation or justification for such an increase. It is argued that the amendments made to the initial legal proposal during the legislative process were not of such type or magnitude to justify such a sharp increase in the amount of fees.

[20] http://ec.europa.eu/health/files/pharmacovigilance/2012-06_concept_paper_en.pdf
[21] http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=COM:2008:0664:FIN:en:PDF

Also, some argue that the fees in the financial statement of 2008 are more closely aligned with those of the NCAs which charge separately for pharmacovigilance activities.

Many respondents from industry argue that the proposed fees are contrary to the objective of the legislation to reduce the costs and the unnecessary administrative burden for the pharmaceutical industry. Some have estimated that the proposed fees would lead to an increase by more than 50% of their budget for fees and, for some pharmaceutical companies, even double this budget. The need for transparency is emphasised, as well as the importance that marketing authorisation holders are not charged twice for the same assessment work. Industry, in particular, flags the risk of possible duplicative fees charged by EMA and NCAs and expects a reduction of national fees whenever work is shifted to the EMA.

The Concept Paper has put forward the possibility of grouping of MAHs for many of the proposed fee types (for the purposes of paying one single fee), as a result of which MAHs would in many cases not need to pay the maximum or full fee. However, the grouping to share the fee for PSUR and PASS assessments was not supported by the vast majority of respondents who argued that this would not work in practice as it would require the sharing of confidential information between MAHs not belonging to the same legal entity (see *2.3. Concept of grouping applied to PSURs, PASSes and Pharmacovigilance Referrals [Consultation items 2, 4 and 6]*).

Many respondents consider that proposed fees would unfairly affect MAHs with a large portfolio of products with well-established safety profiles and many MAs. Such comments come mainly from industry stakeholders representing generics, homeopathics, well-established-use and over-the-counter medicinal products, including allergen manufacturers.

Almost all SMEs express concern about the proposed fee levels, stating that even with the proposed fee reductions, the availability of their products would be under threat.

Many NCAs express criticism that the concept paper lacks information about the distribution of fees to the NCAs acting as rapporteurs and co-rapporteurs during the assessment procedures. On this point, especially industry advocates an analysis of the actual tasks carried out by the EMA secretariat and the NCAs in each instance.

There are also calls for further clarity on how the proposed fees have been established and questions on whether the benchmarks correspond to the scope and volume of documents to be reviewed, activities to be undertaken and number of staff involved; they call for proportionality between the fees and the nature of the work actually carried out. Some respondents acknowledge the difficulty of having a fee adjusted to each individual procedure/product, and rather advocate setting up a single fee or a simple range of fees based on well-defined and justified criteria for each procedure corresponding to the associated workload.

A number of respondents, especially from industry, consider that some pharmacovigilance activities, e.g. referrals and literature monitoring, should be at least partly covered by the EU budget as these activities are linked to the protection of public health.

SUMMARY OF COMMENTS

Fee for assessments of Periodic Safety Update Reports (PSUR)

In general, the principle of charging a fee for the assessment of a PSUR has not been objected to, except when there is a risk of a possible double charging for essentially the same work (e.g. when a PSUR submission would coincide with a renewal assessment). However, the proposed levels of the fee, benchmarked against a Type II Variation procedure, have been criticised, mainly by industry, but also by some National Competent Authorities.

The main criticism to the proposed fee stems from the feeling that benchmarking against a Type II Variation is not fully justified, in order to reflect the real workload associated with the assessment of PSURs. Some replies from industry suggest that the workload of a PSUR assessment is lower than a type II Variation, whereas others from NCAs suggest that the workload could be higher.

Some respondents refer to the need for more precise and transparent cost calculations in order to arrive at the cost of an 'average' assessment. Others would prefer a greater number of levels of fees, based on criteria related to the assessment effort, e.g. the number of ADRs or literature cases (or a reduction for products whose safety profile is well established).

It is also pointed out that the expected number of PSUR assessments should be estimated in relation to the possible effect on the budget of the EMA.

The relevance of using the two-year period following the authorisation as a method of approximation of the assessment workload (and the related fee) is questioned, notably for products where the benefit/risk profile has been well established. In this respect, comments both from industry and NCAs point out that the frequency of PSUR submission, as defined by the EU reference date list, could be taken into account. Many comments argue that the workload in the first two years could actually be higher than afterwards. It is however generally recognised that the administrative complexity of the pharmacovigilance fee system should be minimal.

Some respondents point out that the 'cascade effect' on overall amounts charged to industry for subsequent procedures should be taken into account (e.g. a PSUR leading to a referral leading to a variation).

As an alternative benchmark, the existing renewal fee for a centrally authorised product is often proposed, because considered to require similar workload. Possible duplication of PSUR assessment and renewal assessment for newer products is signalled in this repect. Alternatively, national fee levels are quoted as a potential benchmark, namely fees paid by industry for MRP and DCP products.

Also, as non-CAPs are subject to subsequent national variation fees, concerns are expressed over a possible violation of the principle of equal treatment (of CAPs and non-CAPs).

Fee for assessments of Post Authorisation Safety Studies (PASS)

Overall, the benchmark (Type II Variation) has been questioned and it is argued that the data to be assessed is not comparable, in that a PASS assessment concerns a single report whereas a Type II variation may include several studies and may be more complex, as it may require a revision of several sections of the product information. Where the PASS results lead to an update of the MA of a non-CAP through a variation, for which fees are normally charged, there is concern that MAHs would be charged two separate fees for these activities which are related.

It is proposed that the fee for PASSes should be based on several criteria, such as the methods used for the PASS and the amount and type of data collected; however, to avoid complexity, comments suggest setting a fee or a simple fee range closer to the PASS assessment fee included in the financial statement of 2008.

Especially some respondents from industry express concerns about the discrepancy where no separate variation (and, consequently, no variation fee) will be required in the case of PASS leading to a change in the MA for CAPs, whereas for non-CAPs, a subsequent variation will still be required and charged for.

Concept of grouping applied to PSURs, PASSes and Pharmacovigilance Referrals

While a number of respondents support the concept in general, as a means to reduce the actual amounts to be paid, most of the comments refer to the need to clarify whether MAHs belonging to the same mother company or group of companies (and MAHs having concluded agreements or exercising concerted practices concerning the placing on the market of the medicinal product(s) concerned), should to be taken as 'the same marketing authorisation holder' (as per Commission Communication OJ C 229, 22 July1998). They argue that they should be considered as a single legal entity and that this should not be considered as grouping. In addition, comments state they should not be charged additional administrative fees.

Grouping for submitting PSURs is generally considered very difficult in practice (sharing of commercial data, different standard operating procedures, difficulty to divide the work and to coordinate between different QPPVs, ...), except for entities belonging to the same mother company. In this respect, it is pointed out that producing a single PSUR with all the information, data and analysis coming from independent companies seems unrealistic. Consequently, comments from industry express concern that the anticipated savings through grouping would not materialise in practice.

Some respondents consider grouping for PASSes as an option but draw the attention to some practical/legal constraints. While grouping for the PASSes may facilitate the collaboration between independent MAHs to conduct PASS jointly (as foreseen in the pharmacovigilance legislation), it would require a model-based system for the fee assignment that complies with the principles of proportionality, equal treatment of MAHs and with competition laws. Where PASSes are conducted jointly by different MAHs, it is proposed that the total PASS fee (including any administrative fees) is equally divided amongst all concerned MAHs for the same PASS.

The concept of grouping is considered more relevant in the case of referrals, (where it is already now possible to pay one single referral fee), but several respondents, notably the generics industry, request clarification about how the fee would be divided.

Several respondents consider the administrative fee of 500€ as being too high. Most NCAs consider that the administrative fee should not be retained in full by the EMA.

In some replies it is pointed out that the concept of grouping is not applicable for some specific products, e.g. for allergen extracts.

Pharmacovigilance referrals

The benchmark used, i.e. assessment of initial MA application, is heavily criticised. The proposed fee for pharmacovigilance referrals involving full benefit-risk assessment is considered by many as too high and the work is not considered to be comparable to assessing an initial marketing authorisation application. This is especially underlined by the generics industry. Also, it is pointed out that the assessment of an initial MA is much broader including also non-clinical data and data on chemistry, manufacturing and controls, whereas in the referral, the focus is on the new information that triggered the referral. Recognising that the workload for each referral will vary, some respondents express preference to have one single fee. In any event, there is a general call for better explanation and justification of the workload involved.

Many respondents from the generic industry argue that they are more likely to be subject to several referrals due to their broad portfolio compared to innovator companies, which is claimed to be disproportionate considering the comparative turnovers.

Some respondents suggest a fee reduction for referrals initiated by PRAC within the same class of medicinal products (referring to the same ATC code).

Others consider that if a referral fee will be charged, the amount should be within the range of what is already in place for referrals initiated by MAHs.

Also, some respondents point out that the fact that in addition a Type II variation may be requested, which is also subject to a fee, should also be considered in the referral fee.

As regards payments to the PRAC rapporteurs and co-rapporteurs for their assessments, some respondents refer to the appointment principles laid down in EMA document of 28 June 2012 whereby the co-rapporteurship is automatically granted to the Member State triggering the referrals involving non-CAPs or CAPs/non-CAPs. In view of this, attention is drawn to the risk that referrals could be initiated as a revenue generating exercise, rather than in response to a genuine safety concern.

Some respondents consider that the referrals should be supported at least partly through the EU contribution to EMA.

Pharmacovigilance service fee

Some respondents, notably those representing the larger companies in the innovative sector, argue that the concept of an annual fee might be acceptable for certain well-specified pharmacovigilance activities which constitute a service to the MAHs. However, there is call for more transparency in respect of the tasks which are covered by an annual pharmacovigilance service fee. The fee should also be proportionate to the costs of these activities. At the same time, many respondents from the industry point to the risk of double-charging, as many NCAs already charge annual fees for pharmacovigilance.

Particular concern is expressed by the generic industry, as many of its companies may have a large portfolio (e.g. around 1000 active substances) which would lead to extremely high charges for the proposed pharmacovigilance service fee alone. Similar concerns are expressed by other companies having products with a well-known safety profile which does not change much and generating very few ADR reports) and for companies with low-volume/low sales. They consider that MAHs belonging to the same group of companies (as one legal entity) and acting under one pharmacovigilance system master file should only be required to pay one annual fee per active substance. Some representatives of the generic industry argue for a

reduced fee for generics, as they would not generate the same amount of work as innovator products.

Several respondents consider that the proposed fee unduly favours MAHs with only one medicinal product with several strengths in several Member States, as opposed to MAHs with a broad product portfolio with different active substances but only marketed in a small number of Member States. Some SMEs note that if such a fee is charged, it should be per substance and MAH, without adding charges for additional strengths, formulations or pack sizes.

However, concern is expressed that annual fees are already charged by most Member States for non-CAPs and that there is a risk of multiple charging, if an annual fee is also charged by EMA for the same activities (charging twice for the same work). Assurances are being sought by the industry that the Member States will not charge such a fee if EMA introduces an annual pharmacovigilance service fee.

Some NCAs are questioning the proposed pharmacovigilance service fee. Assuming that there are some 3,500 active substances in the EU in addition to a number of combinations of substances, it is unknown how many MAHs per substance/combination of substances would have to pay the fee. It is claimed that it is therefore not possible to assess if the fee is excessive or appropriate. While several NCAs express support for an annual fee, they consider that the proposed annual pharmacovigilance service fee level is disproportionally high. They also request clarification about what proportion of the fee would be transmitted to the NCAs for the work they carry out.

In addition, some respondents point out that CAPs are currently paying an annual fee of which 30% (ca. 28.770 €) is foreseen for pharmacovigilance and inspection costs. As it is proposed to continue to charge this fee, it is argued that there should be an analysis of the use of the revenue from this fee to ensure that a new annual fee would cover only new activities, which are not covered by the current annual fee.

Many respondents argue that these general pharmacovigilance activities should be at least co-financed by the EU and the Member States.

Some civil society organisations express their disagreement with the proposed service fee as the general activities that are proposed to be covered by this fee do not include support to PRAC members (financial compensation for their participation). They consider that pharmacovigilance fees could also be used to cover the costs of measures that NCAs and patients and healthcare professionals' organisation are taking to encourage patients and healthcare professionals to report suspected ADRs. To cover the costs for these activities, they propose to increase the proposed service fee to 1.250€, to be partially redistributed to NCAs, or to increase the current annual fee proportionally.

ICT tools and services

Some of the respondents support the concept that MAHs should contribute to the general maintenance of EudraVigilance and the PSUR repository. Many industry respondents point out, however, that they have already had to invest heavily in ICT tools and databases to comply with the new pharmacovigilance requirements, thus questioning the need to include ICT services in the annual fee. Also the submission of information (and maintaining the information up to date) on medicinal products by the MAHs to the Article 57(2) database reportedly entails a heavy workload with considerable costs and it is not perceived acceptable to be charged a fee in this context.

Many manufacturers of non-prescription medicines argue against the annual service fee as they consider that companies, which have products with a well-established safety profile and few ADR reports, will hardly benefit from the signal detection of EMA on the basis of EudraVigilance data.

Literature monitoring

Several industry respondents emphasize that they are already required to carry out literature monitoring of their products and that they will not be relieved from this responsibility, despite the fact that EMA will monitor certain substances in selected literature. Therefore, the charging of a fee for this activity is highly questioned as it cannot be regarded as a service to the industry. Moreover, as the EMA literature monitoring will not benefit all companies and products, some respondents argue that it would be unfair to charge all companies for this activity.

Many respondents also argue that the same is true for signal detection in that the MAHs will continue to bear the responsibility for signal detection and evaluation for their products.

Fee incentives for SMEs

In general, the proposal for fee reductions for SMEs and full exemption for microenterprises is welcomed.

Some industry representatives argue that, in addition to the proposed reduced fees for SMEs, there should also be reductions for orphan medicinal products as well as for other low volume/low sales products (to avoid that they may be withdrawn from the market due to the additional pharmacovigilance costs).

Some suggest using a similar methodology as for the MedDRA[22] subscriptions, whereby the companies are charged on the basis of their turnover.

Several respondents request clarification on how SMEs with non-CAPs should apply for SME status at EMA in case a reduced annual fee for SMEs is charged.

Some SMEs consider that further distinction should be introduced between the different types of SMEs, e.g. suggesting that medium-sized SMEs be granted 50% reductions and small SMEs 75%.

Many respondents, particularly from the generic industry, point out that the number of substances or combination of substances of a MAH is not necessarily related to the size of the company, especially when comparing the innovative and generic industry.

Most NCAs argue that they should receive the non-reduced share of the fee, irrespective of the reduction granted to SMEs (or any other reduction).

Other comments

Whilst the 2008 estimations accompanying the legislative proposal are currently outdated, and recognising that the final adopted legislation is not identical to the 2008 proposal, a number of respondents consider that the proposed new amounts should not be completely out of proportion with the 2008 figures.

[22] Medical Dictionary for Regulatory Activities - internatonal medical terminology used to classify adverse event information

There are requests for information about the anticipated revenues for EMA, based on the proposed fees, and how this links with their costs, in order to be able to assess whether the proposed fees are reasonable.

Respondents expect a fair treatment: e.g. an increase in companies' fees budgets which is in proportion with their size; or taking into account the specificity of some products that generate very limited revenues, as argued for instance in the case of diagnostic products or products with a very limited availability.

Whilst the 2008 Financial Statement and Impact Assessment indicated that all costs associated with activities from the proposal should be recouped through fees, a number of respondents, mainly from industry, argue that pharmacovigilance activities should be partially publicly funded. Also, they expect an analysis of the possible effect on EMA's budget.

Most NCAs (national competent authorities) underline the importance of introducing a transparent method for distribution of the fees between the EMA and the NCAs. A significant number of NCAs state that NCA's share should not be affected by any reduction of the fee. Many NCAs request a separate pharmacovigilance inspection fee, in order to pay directly the inspectors from the NCAs that have participated in the inspection. Another suggestion is to introduce fees for (assessing amendments to) risk management plans ('RMPs'), as PRAC will also be involved.

Some respondents also call for an independent arbitration service where there are disputes concerning the fees.

Some organisations representing civil society call for redistribution of pharmacovigilance fees to NCAs, which could give grants to civil society organisations for their participation in pharmacovigilance activities, and to use pharmacovigilance fees to support financially civil society PRAC members.

In addition, there are suggestions to charge fees to cover the development of guidelines and organising public hearings.

ANNEX 3 – PHARMACOVIGILANCE ACTIVITIES AT EU LEVEL: SHORT DESCRIPTION AND ESTIMATED COSTS

The revised pharmacovigilance legislation[23] introduced a wide range of changes to the EU system of pharmacovigilance with implications both for the pharmaceutical industry as well as for the competent authorities. This Annex outlines the activities which imply the involvement of EMA, including rapporteurs from the MS.[24]

The costs of the pharmacovigilance activities at EU level and, where applicable, of the MS acting as rapporteurs are estimated in Table 6. They are divided into four categories, (1) costs for assessment of PSURs[25], (2) costs for assessment of PASSs[26], (3) costs for assessment in the framework of Pharmacovigilance Referrals and (4) other costs of the EMA which cannot be directly linked to any of the three above procedures.

The overall estimated cost for these activities is € 38.5 mil. Of this figure, € 28 mil. (ca. 73 %) amount for the direct cost to the EMA and € 10.5 mil. (ca. 27 %) represent the cost of the NCA with respect to their responsibilities of conducting the scientific work as rapporteurs.

The cost of procedure-based activities (PSURs, PASS and Pharmacovigilance Referrals) amounts to € 11.3 mil, € 1.5 mil. and € 6.7 mil. respectively. In overall amounts, this corresponds to:

- € 9.2 mil costs of the EMA
- €10.3 mil costs of the MS rapporteurs

The cost for other pharmacovigilance activities of the EMA not directly linked to any of the above procedures is estimated at € 19.1 mil.

These figures, as well as estimations of the number of chargeable units in terms of MAH, MA and EVcodes[27] serve as a basis for calculating the fees to be charged by the EMA for the pharmacovigilance activities as well as for the purposes of assessment of different options to collect the fees. This is dealt with in Annex 4.

With regard to the administrative costs for the actual collection of the fees, Table 7 below outlines the number of envisaged transactions per EV-code, number of envisaged invoiced parties as well as estimated costs for such activities. EMA has not yet implemented the registration of entitlements outside the financial system with monthly reconciliation. Option 2 would require this level of web-based automation and is envisaged to be introduced in 2014/2015. Thus, no additional cost to include an annual pharmacovigilance flat fee is expected. The same automation would also be attractive for option 3 despite the fact that

[23] Regulation (EU) No 1235/2010 amending Regulation (EC) No 726/2004 and Directive 2010/84/EU amending Directive 2001/83/EC

[24] The pharmacovigilance activities introduced by the revised legislation on pharmacovigilance are undertaken by the EMA and scientific evaluation within these EU procedures is performed by the rapporteurs and co-rapporteurs from the NCAs appointed for the individual procedures. Rapporteurs should be remunerated by the EMA for the work that they provide.

[25] Periodic Safety Update Reports

[26] Post-Authorisation Safety Studies

[27] See Annex 1

options 3 might be administratively more complicated. The additional fee processing for multiple MAH per procedure is estimated at € 450 000. The estimated administrative costs are added to figures on pharmacovigilance activities and are calculated in under each option in Annex 4.

Pharmacovigilance activities et EU level – some basic explanations

Database of medicinal products for human use authorised in the EU ('Article 57(2) database')

Marketing-authorisation holders were required to submit electronically to the EMA information on all human medicines authorised in the EU by 2 July 2012. Current non-validated data from the database suggests that there are in total some 9000 active substances/combination of substances in the EU (approximately 50% of these are authorised only in one MS and 50% in more than one MS). Information included in this database is used for the purposes of calculating the fees and it is proposed that the EMA use records in the same database to underpin its invoicing activities.

Reporting of Adverse Drug Reaction (ADRs)

Under the previous system, marketing authorisation holders submitted adverse reaction reports to the NCAs and in some cases also to the Eudravigilance (EV) database held by the EMA, depending on the route of authorisation, the seriousness of the reaction and the type of reporter. With the revised pharmacovigilance legislation, this system has been streamlined and it is foreseen that once the EV database has achieved its full functionality, all reports will be sent by marketing authorisation holders to the EV database only (during the current transitional phase, the reports are also sent to the MS).

The MAHs previously had the responsibility to monitor the literature for reports of ADRs and subsequently submit the reports. In future, the EMA will monitor selected active substances in selected medical literature and will also enter the ADRs found in this literature into the EV database. It is thus expected to reduce the number of duplicate entries.

Periodic Safety Update Report (PSUR) requirements

Previously a PSUR would be submitted on regular intervals to all the national competent authorities where the same medicinal product was authorised, followed by an outcome of the assessment from each of the NCAs involved. Those PSURs and the related assessment reports were to a large extent repetitive. Some NCAs charge a specific fee for the submission of PSURs whilst others include it in their national annual fee (see Table 1 in the main part of this impact assessment report for some indicative information).

With the revision of the legislation, this has changed as the PRAC has established reference dates and submission frequencies for products with the same active substance or combination of active substances, where this substance (or combination of substances) is authorised in more than one MS. The European Reference Date list ('EURD" list, see Annex 1 for a brief explanation) that has been published by the EMA in October 2012 will take partially effect on 1 April 2013 and is expected to be fully applicable by the time when fees for pharmacovigilance will be introduced. It currently contains some 3350 entries corresponding to active substances and combination of substances, as a result of which approximately 600 substances (or combinations) are subject to PSUR submission annually (on average). An EU-

wide single assessment procedure will apply to PSURs submitted by the MAHs according to the EURD list (one submission) and will result in a single outcome of such an assessment. Generic, well established use, homeopathic and traditional use herbal products use are, under the 2010 pharmacovigilance legislation, exempted from submitting PSURs (as these products are considered to have a well-established safety profile), unless obligations to the contrary are specified as conditions to the marketing authorisation, the submission is requested by the competent authority and the products are specifically included on the EURD list of harmonised submissions. Currently, approximately 10% of all the active substances/combination of substances included in the current EURD list, require PSUR submissions also for generics. Overall, this new EU-wide procedure for the assessment of PSURs will greatly decrease the workload for the MAHs as well as the administrative burden of supplying PSURs to different MSs and paying the corresponding fees.

Oversight and submission of Post-Authorisation Safety Studies (PASS)

The EMA will be involved in approval of protocols, amendments to the protocols and in the assessment of the study reports conducted in the post-authorisation phase. The requirement relates to non-interventional studies involving safety data from patients or healthcare professionals where the studies have been requested as an obligation to the initial marketing authorisation or as an obligation to the marketing authorisation in the post-authorisation phase, where the study will be conducted in more than one MS. In respect of obligations to conduct studies imposed after the granting of the marketing authorisation, the 2010 pharmacovigilance legislation encourages MAHs to submit joint studies if the same concern about the risk of an authorised medicinal product relates to more than one medicinal product.

Pharmacovigilance referrals

A pharmacovigilance referral is a centralised procedure used to resolve concerns over the safety of a medicine or a class of medicines. A referral resulting from the evaluation of pharmacovigilance data will always involve the PRAC and can be triggered either when 'EU interest' is considered to be involved or under the new 'Urgent EU procedure'. It is proposed that a pharmacovigilance referral fee is charged in any of these cases as the procedure will be the same.

Estimation of the costs for pharmacovigilance activities at EU level

The costs of the pharmacovigilance activities within the responsibilities of the EMA are estimated in Table 6.

The administrative costs of invoicing the pharmacovigilance activities for the various options considered are estimated in Table 7.

Table 8 provides details of the background data on which the estimates are based.

Table 6: Estimation of costs for Union-wide pharmacovigilance activities (in EUR)

Activities					EMA staff				NCA staff				Total costs EMA + NCAs
					No. of hours required	Tarrif per hour / hourly wage	Estimated Frequency per year	**Overall cost**	No. of hours required	Tarrif per hour / hourly wage	Estimated Frequency per year	Overall cost	
PSUR	1			Preparation of list of harmonised submission dates for selected active substances	53,75	124,1	2	€13 341					
	2			Preparation of PRAC advice and updated EURD list following request for changes from MAH3	21,5	124,1	10	€26 682					
	3			Validation of PSUR, preparation of data for Rapporteur from Eudravigilance database and other sources4	11,9	124,1	600	€886 074					
					5,1	79,5	600	€243 270					
	4			Preparation of PRAC, CHMP/CMDh outcome	21,2	124,1	600	€1 578 552					
					9,1	79,5	600	€434 070					
	5			PRAC Staff time related to PSUR	81	124,1	11	€110 573	194	109	11	€232 606	
					81	79,5	11	€70 835					
	6			CHMP/CMDh Staff time related to PSUR	27	124,1	11	€36 858	32	109	11	€38 368	
					40,5	79,5	11	€35 417					
	6a			Actual evaluation/assessment of PSUR applications by NCAs - activity of raporteurs					116	109	600	€7 586 400	
								€3 435 671				**€7 857 374**	**€11 293 045**
PASS	7		PASS Protocol	Preparation of request including scientific questions and pre-submission meeting	25	124,1	35	€108 588					
	8			Summary outcome of protocol and outcome documents for PRAC	42,5	124,1	35	€184 599					
	9			Summary outcome of protocol amendments and outcome documents for PRAC3	27,5	124,1	35	€119 446					
	10			Summary of study report and outcome of report documents for PRAC and CHMP/CMDh4	60	124,1	35	€260 610					
	11			PRAC Staff time related to PASS	54	124,1	11	€73 715	130	109	11	€155 870	
					54	79,5	11	€47 223					

					27	124,1	11	€36 858	32	109	11	€38 368	
	12			CHMP/CMDh Staff time related to PASS	40,5	79,5	11	€35 417					
	12a			Actual evaluation/assessment of PASS applications by NCAs - activity of raporteurs					116	109	35	€442 540	
								€866 456				**€636 778**	**€1 503 234**
Pharmacovigilance Refferals			Initiation	Preparation of procedure including scope of procedure, identification of products involved, List of Questions, analyses of in-house data1	73,8	124,1	40	€366 343					
	13				73,8	79,5	40	€234 684					
			Assessment	Preparation of outcome documents for PRAC and CHMP/CMDh (temporary measures, list of outstanding issues, recommendations, opinions), analyses of in-house data, organisation of oral explanations, scientific advisory groups/expert meetings and public hearin	300	124,1	40	€1 489 200					
	14				300	79,5	40	€954 000					
			post - assessment	Preparation and publication of information on webportal, communication, translations, access to document requests and re-examinations as applicable3	193,75	124,1	40	€961 775					
	15				193,75	79,5	40	€616 125					
					54	124,1	11	€73 715	130	109	11	€155 870	
	16			PRAC Staff time related to referrals	54	79,5	11	€47 223					
					54	124,1	11	€73 715	65	109	11	€77 935	
	17			CHMP/CMDh Staff time related to referrals	81	79,5	11	€70 835					
	17a			Actual evaluation/assessment of Refferals applications by NCAs - activity of raporteurs					360	109	40	€1 569 600	
								€4 887 616				**€1 803 405**	**€6 691 021**
	18	Literature monitoring		Outsourced literature monitoring and entering of data in EudraVigilance	8153	124,1	1	€1 011 787					
	19			Quality control of the outsourced activities and entered data	4455	124,1	1	€552 866					

		ICT		IT development and software maintanace				€4 882 643					
Others				IT infrastructure maintanace				€2 061 636					
	22	Signal detection + ADRs handling + risk management		Scientific validation of product and substance data submitted by the MAHs (outsorced)	22390	124,1	1	€2 778 599					
				Clinical validation of signals, signal management by scientific staff and provision of analysis from EudraVigilance database and other data sources at the request from MS	10 197	124,1	1	€ 1 265 455					
	23				2 499	79,5	1	€ 198 670					
				Management of RMPs including procedural support through PRAC, monitoring the outcome of risk minimisation measures and preparation of documents for publication for CAPs and for NAPs at the request of a member state.	17820	124,1	1	€2 211 462					
	24				6534	79,5	1	€519 453					
	25			Monitoring the effectiveness of public health measures (e.g. risk management systems, through outsources studies of their outcomes using longitudinal patient databases).	7643	124,1	1	€948 496					
				Pharmacovigilance inspections, information gathering on non-compliance and follow-up	6534	124,1	1	€810 869					
	26				3861	79,5	1	€306 950					
	27			Translations of communication related material and of data received from the public in relation to referrals	3370	124,1	1	€418 217					
					891	124,1	1	€110 573					
	28			PRAC Staff time (remaining)	891	79,5	1	€70 835					
	29			PRAC meeting costs				€564 503	194	109	11	€232 606	
	30			CHMP meeting costs				€112 901					
								€18 825 914				**€232 606**	**€19 058 520**
				Total costs for Pharmacovigilance				**€28 015 657**				**€10 530 163**	**€38 545 820**

Source: SANCO/EMA

* EMA hours required for a given activity are weighted averages of min/max workload as estimated by the EMA based on the likelihood of procedures being minimum or maximum labour intensive; average EMA staff costs are calculated on the basis of EMA basic data sheet (Table 8 of this Annex)

** Cost estimations of the rapporteurs from NCAs are based on a pilot costing exercise of NCAs from 2009 attempting to assess the real costs of MS rapporteur's scientific evaluations; in the current costing, it was assumed that time spent on PSURs / PASS assessment will on average be equal to the average time spent by NCA rapporteurs on Renewals

in the centralised procedure and the average time spent on Pharmacovigilance Referrals will be equivalent to the average of time spent on "abridged application" and "full application" for a centralised MA as declared in the 2009 exercise. Average personnel cost per hour reported by the participating NCAs (i.e. € 100.5) was adjusted taking into account the inflation as reported by Eurostat for 2010 -2012 (i.e. 2.1 %, 3.1 % and 3 % respectively).

*** PRAC/CHMP meeting costs are calculated assuming that one MS representative per meeting is sufficient

[1] Includes: preparation of list of substances and sending it to NCAs, consolidation of comments and timeframes and sending consolidated list to NCAs, finalisation of list including identified issues, PRAC review, sending list to CHMP and CG and publication of list.

[2] Includes: preparation of outcome i.e. PRAC advice and updated list, following CHMP/CMDh discussion and publication of revised list if applicable.

[3] Includes: technical validation (depending on number of PSURs per assessment), preparation of data for rapporteurs in the form of analyses of EU data-sources, notably EudraVigilance ADR data, liaison with MAH(s).

[4] Check of assessment report for confidential information and redaction if necessary, arranging oral explanation for the PRAC if necessary, preparation of PRAC recommendation (depending on number of PSURs per assessment), arrange oral explanation for the CHMP if necessary, preparation of CHMP opinion, preparation of web portal documents and preparation of translations.

[10] Includes: preparation of summary report, preparation of PRAC LoQs if applicable and outcome documents and attending PRAC plus preparing outcome documents CHMP/CMDh if applicable and attending CHMP/CMDh discussion on report if applicable.

[14] Includes: preparation of temporary measures, SAG/expert meetings , arranging oral explanation for the PRAC if necessary, preparation of PRAC recommendation, analyses of in-house data, public hearings if necessary, arrange oral explanation for the CHMP if necessary, preparation of CHMP/CMDh opinion if applicable, document management of submissions from various stakeholders including the public following announcement of the referral and if applicable following the public hearing, interaction with stakeholders (MAHs, patients, HCP, investigators).

[20,21] Estimate of IT costs includes both the IT projects and IT Infrastructure (Eudravigilance, PSUR, signal detection, transparency, technical aspects and others) as projected by SANCO IT unit; the costs are calculated as average IT annual costs from the projected period of 2012-2016

Table 7: Estimation of administrative cost of invoicing the pharmacovigilance activities per EV-code

		Option 1 - no PhV fees	Option 2 - flat fee	Option 3 - procedure based fee and flat fee	Option 4 - only procedure based fee	*Assumptions*
Flat fee	Transactions	0	359883	359883	0	*based on EV-CODE*
	Invoiced parties	0	10826	10826	0	
PSUR	Transactions	0	0	33600	33600	*600 PSURs * 56 EV-CODEs*
	Invoiced parties	0	0	1800	1800	*600 PSURs * 3 MAHs*
PASS	Transactions	0	0	35	35	*35 PASS*
	Invoiced parties	0	0	35	35	*35 PASS * 1 MAH*
Referral	Transactions	0	0	4280	4280	*40 Referrals * 107 EV Codes*
	Invoiced parties	0	0	1440	1440	*40 Referrals * 36 MAH*
Total	**Transactions**	**12952***	**359883**	**397798**	**37915***	
	Invoiced parties	**5828**	**10826**	**14101**	**3275**	
Costs	AD staff	€67 150	€0	€196 570	€196 570	
	AST staff	€86 059	€0	€251 926	€251 926	
	Total	**€153 209**	**€0**	**€448 496**	**€448 496**	
		Covers all EMA fee transactions in 2012	Web-based automation is envisaged for EMA flat fee transactions in 2014/15, with negligible additional cost to include the new pharmacovigilance flat-fee	Additional fee processing for multiple MAH per procedure require estimated 1 AD and 2 AST staff. Average time needed per fee transaction on an invoice is 8 min.	Fee processing for multiple MAH per procedure require estimated 1 AD and 2 AST staff. Average time needed per fee transaction on an invoice is 8 min.	
ICT requirements			Web-based automation for invoicing/pre-payment	Web-based automation for invoicing/pre-payment		
			1 financial transaction (manual per month) as per FFR	Adaption of SAP interface and/or use of automation above	Adaption of SAP interface and/or use of automation above	

			Development in SAP to allow for procedure based transactions. Current system is set up for 1:1 procedure:MAH, option would assume 1:many procedure:MAH	Development in SAP to allow for procedure based transactions. Current system is set up for 1:1 procedure:MAH, option would assume 1:many procedure:MAH	
			Development in SAP to allow for different fee per invoiced party per procedure + increased administraive burden for processing and changing thereof.	Development in SAP to allow for different fee per invoiced party per procedure + increased administraive burden for processing and changing thereof.	

Source: EMA

* Estimated 37,915 fee transactions for the procedure-based pharmacovigilance fees. This represents approximately a three-fold increase to the current volume of all EMA fee transactions of 12,952 (2012)

Table 8: EMA basic data sheet used for calculations of the costs for Pharmacovigilance activities

1. Productive working days/year	**2012**	**2016**
Number of days/year	366	365
- less weekends	-105	-104
- less bank holidays	-18	-17
- less average leave days	-29	-29
- less average sick leave days	-9	-9
- less average training days	-7	-7
Total number of productive days/year	**198**	**199**
2. Standard working hours/year	**2012**	**2016**
Standard working hours/day	8 *	8 *
x number of productive days/year	198	199
Total number of productive hours/year	**1,584**	**1,592**
3. Average staff cost	**2012**	**2016**
Average salary items AD (~ AD8)	138,579	142,655
Overhead non-salary cost, building, equipment etc.	38,304	32,415
Overhead for support and management (as per ABB)	19,687 *(11.13%)*	19,223 (*10.98%)*
Total staff cost AD	**196,570**	**194,293**
Average salary items AST (~ AST3)	75,043	77,250
Overhead non-salary cost, building, equipment etc.	38,304	32,415
Overhead for support and management (as per ABB)	12,616 *(11.13%)*	12,041 (*10.98%)*
Total staff cost AST	**125,963**	**121,706**
Average salary items Contract Agent (~ FG III)	48,538	53,360
Overhead non-salary cost, building, equipment etc.	38,304	32,415
Overhead for support and management (as per ABB)	9,666 *(11.13%)*	9,418 (*10.98%)*
Total staff cost Contract Agent	**96,508**	**95,193**
Notes:	**2012**	**2016**
Weighting on salary items assumed (including exchange rate)	148	130
Employers pension contribution included	no	yes

Source: EMA

* A working week of 40 hours is applied to all calculations which already corresponds to the current reality and workload.

ANNEX 4 – CALCULATION OF THE AMOUNT OF FEES FOR CONSIDERED OPTIONS

This Annex outlines the calculations of the amount of the fees for each considered option. The calculations are based on the estimated costs of the pharmacovigilance activities outlined in Annex 3 and on the basic data estimations in Table 9 below.

When a fee taking into account SMEs reduction is calculated, it is assumed that the micro-enterprises will be entirely exempted from the obligation to pay any pharmacovigilance fee whereas the small and medium-sized enterprises will pay 60% of the standard fee. Further detailed information on the numbers and breakdown of SMEs, how they would be impacted and justification for their potential exemption is provided in Annex 5.

When a fee taking into account the reductions foreseen for certain categories of medicinal products[28] is calculated, it is assumed that the reduction of 20 % from the standard fee will apply to generics. The reduction for generics is applicable only to calculations related to any flat fee.

Table 9: Basic data

Total number of MAH in EU	10 826
Number of MAH of a medicinal product with active substance authorised in more than 1 MS*	9727
Total number of active substances in corresponding to authorised products in the EU	8 869
Number of active substances for which PSURs are required (EURD list)	3 357
Total number of EV-codes in the EU	383 395
Number of EV-codes for active substances on the EURD list	359 883
- EV-codes corresponding to generic products	49%
- EV-codes corresponding to originator products	51%
Number of EV codes for active substances on EURD list for which PSUR is required[29]	189124
Total number of MA in EU	288 133
Number of MA for active substances on the EURD list	267 780
SMEs out of the total number of MAH	90 %
Micro-enterprises out of SMEs	33 %
EV-codes / MA held by SMEs	10%
EV-codes / MA held by micro-enterprise (out of SMEs)	25%

Source: Art 57 database as of February 2013 (data under validation); EMA SMEs register; EMA database of centrally registered products

*Estimate based on cross-reference data extracts.

[28] Includes authorised generic, homeopathic and herbal medicinal products as well as medicinal products authorised on grounds of well-established medical use.

[29] EV codes of generic medicinal products are included for 10% of the substances.

Option 2: One flat fee covering all pharmacovigilance activities

The costs of all Union-wide pharmacovigilance activities carried out in one are estimated at € 38.5 mil. In order to cover these costs through a single annual flat fee, three scenarios are considered.

(A) Fee charged per Marketing authorisation holder (MAH)

(B) Fee charged per EV-code

(C) Fee charged per Marketing authorisation (MA)

Table 10: Calculation of a single annual flat fee

Chargeable unit	unit no.	standard fee (no reductions)	fee taking into account SMEs reduction	fee taking into account generics reduction	cost of SME reduction	cost of generics reduction
(A) MAH	9727	€3 963	€8 581	n.a.	€20 745 360	n.a.
(B) EV-CODE	359883	€107	€113	€122	€2 126 498	€5 559 233
(C) MA	267780	€144	€152	€165	€2 120 020	€5 542 298

Source: own calculations based on data from EMA

The most favourable scenario for this option is considered to be the fee paid on the basis of EV-codes and taking into account the reduction of 40 % for SMEs as well as the 20 % reduction for generics which are not held by SMEs. The micro-enterprises would be exempted from paying the fee.

Despite the fact that fee determination when charging per MAH would be simple and straightforward, it would not respect the fairness principle, as the differences between the MAH and the number of products and presentations would not be taken into account. It would therefore not capture (even indirectly) the market share of the companies. Moreover, the

calculations show that the fees charged by MAHs would stay beyond any reasonable proportions, i.e. in the case when reductions apply, the SMEs would have to pay more than if a standard fee without the reduction would be applied.

Option 3: A combination of separate fees for procedure based activities and a flat fee for all other activities

Periodic safety update reports (PSUR)

The overall annual cost of pharmacovigilance activities related to the assessment of PSURs is estimated at € 11.3 mil. The average cost of a PSUR assessment is estimated at € 18 822. In order to cover these costs through a fee, three scenarios per PSUR assessment are considered.

(A) Fee charged per Marketing authorisation holder (MAH)

(B) Fee charged per EV-CODE

(C) Fee charged per Marketing authorisation (MA)

Table 11: Calculation of PSUR fee

Chargeable unit	average no. / PSUR	standard fee	fee taking into account SMEs	fee taking into account generics reduction	cost of SME reduction	cost of generics reduction
(A) MAH	3	€6.496	€14.066	n.a.	€12.400	n.a.
(B) EV-CODE	56	€334	€354	€390	€1.035	€2.711
(C) MA	42	€449	€476	€524	€1.035	€2.711

Source: own calculations based on data from EMA

The most favourable scenario for this option appears to be the fee paid on the basis of EV-codes and taking into account the reduction for SMEs. The reductions for generics is questionable as in principle all companies should bear the costs of potential safety concerns usually associated with PSUR procedure, once it has been decided to require PSURs for generics through the EURD substances list.

In practice however, charging per EV-code might lead to a very high variability in the fee revenue per procedure[30] causing disproportionality and unpredictability of revenues. That is why the most reasonable scenario is to charge a fixed overall amount of € 18 822 per procedure increased for the administrative costs of actual fee collection of € 662 and to use EV-codes for the distribution of the fee among the MAHs. Given that the PSURs submission is specified in the EURD list, the MAHs will have sufficient information well in advance as to when they will be subject to the procedure.

Post-authorisation safety studies (PASS)

The overall annual costs of pharmacovigilance activities related to the assessment of PASSs are estimated at € 1.5 mil. The average cost of a single PASS assessment thus amounts to € 42 950. These estimations are based on 35 PASS per year. In order to cover these costs through a fee, it is reasonable to charge the fee per procedure, increased by the administrative cost for actual collection in the amount of € 12 per PASS and divide this figure by the number of entities taking part in the conduct of the study. The number of entities will depend on the arrangements among the marketing authorisation holders for each case.

Pharmacovigilance Referrals

The overall costs of activities related to the assessment in case a pharmacovigilance referral are estimated annually at € 6.7 mil. The average cost of a pharmacovigilance referral assessment is estimated at € 167 276. This is based on 40 estimated Referrals per year. In order to cover these costs through a fee, three scenarios are considered.

(A) Fee charged per Marketing authorisation holder (MAH)

[30] Certain substances with a large number of EV-codes associated (e.g valsartan, simvastatin, among others) could lead to collecting a revenue of ca. € 1.5 m per single PSUR assessment. Other substances (e.g. triclosan, heparin among others) could amount to a revenue of only € 668 per single PSUR assessment.

(B) Fee charged per EV-CODE

(C) Fee charged per Marketing authorisation (MA)

Table 12: Calculation of pharmacovigilance referral fee

Chargeable unit	Av No. / active substance	standard fee	fee taking into account SMEs	fee taking into account generics reduction	cost of SME reduction	cost of generics reduction
(A) MAH	3	€57 730	€125 012	n.a	€100 114	n.a.
(B) EV-CODE	56	€2 969	€3 142	€3 464	€10 455	€25 352
(C) MA	42	€3 995	€4 227	€4 660	€10 455	€25 352

Calculations based on data from EMA

The most favourable scenario for this option seems to be a fee paid on the basis of EV-codes and taking into account the reduction for SMEs. The reductions for generics is questionable as in principle all companies should bear the costs of potential safety concerns usually associated with a pharmacovigilance referral.

In practice, however, this might lead to a very high variability in the fee revenue per single procedure due to impossibility to estimate the real number of MAHs involved in it. As a consequence, charging an amount per EV-code would lead to disproportionality and unpredictability of revenues.

That is why the most reasonable scenario is to charge a fixed overall amount of € 167 276 per procedure, increased by € 1266 of administrative costs, and to divide the fee among the MAHs based on the actual number of MAH taking into account the number of EV-codes that they hold.

Non-procedure based activities

The costs of the pharmacovigilance activities not directly related to any of the three procedures above are estimated annually at € 18.8 mil. In order to cover these costs through an annual flat fee, three scenarios are plausible.

Table 13: Calculation of a flat fee for a non-procedure based activities

Chargeable unit	unit no.	standard fee (no reductions)	fee taking into account SMEs reduction	fee taking into account generics reduction	cost of SME reduction	cost of generics reduction
(A) MAH	9727	€1 935	€4 191	n.a.	€12 402 513	n.a.
(B) EV-CODE	359883	€52	€55	€60	€1 038 589	€2 715 149
(C) MA	267780	€70	€74	€80	€1 035 425	€2 706 878

Calculations based on data from EMA

The most favourable scenario for this option is considered to be the fee paid on the basis of EV-codes and taking into account the reduction of 40 % for SMEs as well as the 20 % reduction for products with well-established safety profile such as generics which are not held by SMEs. The micro-business would be exempted from paying that fee.

Despite the fact that fee determination when charging per MAH would be simple and straightforward, it would not respect the fairness principle, as the differences between the MAH and the number of products and presentations would not be taken into account. It would therefore not capture (even indirectly) the market share of the companies.

Option 4: Procedure based fees only

The overall cost of Union-wide pharmacovigilance activities carried out in one year, estimated at € 38.5 mil (i.e. € 19.5 mil procedural related costs + € 19 mil. other costs), would be covered entirely through the fees collected from the three procedures, i.e. PSUR, PASS and Pharmacovigilance Referral. In common with the previous options, there are three scenarios for collecting the fees. Moreover, two different possibilities of attributing the non-procedure related costs to the procedures are considered.

(1) Non-procedure related costs equally distributed among the three types of procedures

(2) Non-procedure related costs proportionally distributed among the three types of procedures, based on the workload involved within each type of procedures

Periodic safety update reports (PSUR)

The overall cost of pharmacovigilance activities related to the assessment of PSURs is estimated annually at € 11.3 mil. In case of attributing the proportion of non-procedure related costs in addition, the cost for assessment of PSURs would increase to € 16.2 mil. when distributing equally or to € 19.9 mil. when distributing proportionally. The average cost of a single PSUR assessment would thus amount to € 27 053 or € 33 132 respectively. This is based on estimated 600 PSURs per year. In order to cover these costs through a fee, three scenarios per PSUR assessment are considered.

Table 14: Calculation of a PSUR fee increased by costs of non-procedure based activities

Chargeable unit		average no. / PSUR	standard fee	fee taking into account SMEs	fee taking into account generics reduction	cost of SME reduction	cost of generics reduction
(1) equal distribution	(A) MAH	3	€9 120	€19 486	n.a	€15 646	n.a.
	(B) EV-CODE	56	€522	€557	€614	€1 838	€4 457
	(C) MA	42	€702	€749	€827	€1 838	€4 457
(2) proportional distribution	(A) MAH	3	€11 544	€24 667	n.a.	€19 806	n.a.
	(B) EV-CODE	56	€661	€705	€778	€2 327	€5 642
	(C) MA	42	€889	€948	€1 046	€2 327	€5 642

Calculations based on data from EMA

The proportional distribution of the non-procedure related costs within the fee is considered as the most suitable and fair option. The most favourable scenario for this option seems to be a

fee paid on the basis of EV-codes and taking into account the reduction for SMEs. The reduction for generics is questionable as in principle all companies should bear the costs of potential safety concerns usually associated with PSUR procedure, once it has been decided to require PSURs for generics through the EURD substance list.

In practice, however, this might lead to a very high variability in the fee revenue per procedure[31] causing disproportionality and unpredictability of revenues. That is why the most reasonable scenario is to charge a fixed overall amount of € 33 132 per procedure increased by the administrative costs of fee collection of € 662 and divide the fee among the MAHs based on the proportion of EV-codes for each MAH. Given that the PSURs submission is specified in EURD list, the MAHs will have sufficient information well in advance as to when they will be subject to the procedure.

Post-authorisation safety studies (PASS)

The overall cost of pharmacovigilance activities related to the assessment of PASSs is estimated annually at € 1.5 mil. In case of attributing the proportion of non-procedure related costs in addition, the cost for assessment of PASS would increase to € 7.8m when distributing equally or to € 3m when distributing proportionally. The average cost of a single PASS assessment would thus amount to € 224 459 or € 84954 respectively. This is based on 35 estimated PASS per year. In order to cover these costs through a fee, considering the proportional distribution of the non-procedure related costs within the fee as the most suitable and fair option, the fee per procedure would amount to € 84954, adding the €12 for administrative costs and dividing this figure by the number of entities taking part in the conduct of the study. The number of entities will depend on the arrangements among the marketing authorisation holders for each case.

Pharmacovigilance referrals

The overall costs of pharmacovigilance activities related to the assessment in case of a pharmacovigilance referral are estimated annually at € 6.7 mil. In case of attributing the proportion of non-procedure related costs in addition to this, the costs for referrals would increase to € 13m when distributing equally or to € 13.2m when distributing proportionally. The average cost of a referral would thus amount to € 326 097 or € 330870 respectively. This is based on estimated 40 pharmacovigilance referrals per year. In order to cover these costs through a fee, three scenarios are considered.

[31] Certain substances (e.g. valsartan, simvastatin) could lead to a revenue of € 3.4m per PSUR assessment. Other substances (e.g. triclosan, heparin) could cause the fee revenue to drop to only € 1400.

Table 15: Calculation of a Pharmacovigilance referral fee increased by cost of non-procedure based activities

Chargeable unit		Av No. / active substance	standard fee	fee taking into account SMEs	fee taking into account generics reduction	cost of SME reduction	cost of generics reduction
(1) equal distribution	(A) MAH	3	€112 543	€243 705	n.a.	€195 169	n.a.
	(B) EV-CODE	56	€5 788	€6 125	€6 752	€20 381	€49 422
	(C) MA	42	€7 787	€8 240	€9 084	€20 381	€49 422
(2) proportional distribution	(A) MAH	3	€114 191	€247 273	n.a.	€198 026	n.a.
	(B) EV-CODE	56	€5 873	€6 215	€6 851	€20 679	€50 145
	(C) MA	42	€7 901	€8 361	€9 217	€20 679	€50 145

Calculations based on data from EMA

The proportional distribution of the non-procedure related costs within the fee is considered as the most suitable and fair option. The most favourable scenario for this option would be a fee paid on the basis of EV-codes and taking into account the reduction for SMEs. The reduction for generics is questionable as in principle all companies should bear the costs of potential safety concerns usually associated with a pharmacovigilance referral procedure.

In practice however, this might lead to a very high variability in the fee revenue per actual procedure due to impossibility to estimate the real number of MAHs involved in it. As a consequence, charging an amount per EV-code would lead to disproportionality and unpredictability of revenues.

That is why the most reasonable scenario is to charge a fixed overall amount of € 330 870 per procedure and active substance, increased by € 1266 of administrative costs, and to divide the fee among the MAHs based on the real number of MAH taking into account the proportion of EV-codes that they hold .

GROUPING FOR THE PURPOSES OF PHARMACOVIGILANCE FEES

The public consultation paper had put forward for discussion the assumption that MAHs concerned by one assessment would form a group and that the fee would be shared among members of the group.

While a number of respondents supported the concept in general, as a means to reduce the actual amounts to be paid, most of the comments considered the concept to be very difficult to apply in practice. It was referred to the need to clarify whether MAHs belonging to the same mother company or group of companies, MAHs having concluded agreements or exercising concerted practices as regards the placing on the market of the medicinal product(s), should be taken as 'the same marketing authorisation holder' (as per Commission Communication OJ C 229, 22 July1998).

On the other hand, it should be noted that the EMA has experience with grouping only for the purpose of active participation in referral procedures as such and it is unclear whether the possible grouping for the payment of a fee would follow the same pattern. Moreover, there is currently no available structured information on the ownership relationship amongst MAH

throughout the EU, which could have been used as a possible indicator to estimate the degree of grouping for the payment of a given type of fee. This uncertainty makes it virtually impossible to predict with any degree of precision how MAH would possibly group for the payment of fees.

These consideration lead to the following orientations per procedure, which are relevant to the estimation of the fee levels and to the way fees would be charged.

PSUR assessment

Following feedback that was received during the public consultation, grouping for submitting PSURs is considered very unlikely in practice (sharing of commercial data, different standard operating procedures, difficulty to divide the work and to coordinate between different QPPVs, etc.), except for entities belonging to the same mother company. In this respect, producing a single PSUR with all the information, data and analysis coming from independent companies seems unrealistic. This leads to an uncertainty over the number of products and MAH concerned by one PSUR, as well as an uncertainty over the number of individual PSURs submitted in the framework of a single PSUR assessment of a given substance. It is therefore reasonable to lower the level of the chargeable unit (and, respectively, the unit for the calculation of the applicable fee) from the entire procedure to MAHs or authorisations. For the sake of predictability and proportionality, a minimum and a maximum total amount that the EMA should collect per PSUR assessment could be foreseen in order to avoid extremes. This approach was explored in the different options, however the results of it would not be in line with the objective of a cost-based fee and practical difficulties of setting the minimum and maximum levels arise. This would ultimately increase the uncertainty of funding the pharmacovigilance activities, as the distribution of active substances, the number of EV-codes involved, the number of MAHs involved and the relationship between these variables can not be established with a sufficient degree of precision. Consequently, the preferred approach is to distribute the amount of the fee among the MAHs involved proportionately to the respective number of chargeable units.

PASS assessment

Respondents to the public consultation considered grouping for PASS as an option but draw the attention to some practical/legal constraints (e.g. a PASS is imposed on one MAH but the study is conducted by several MAH jointly). Therefore, where PASS are conducted jointly by different MAHs, it is reasonable to keep the charging at the level of the procedure, i.e. the assessment of the study, as the number of MAH or the number of MA in their portfolio would not have a significant impact on the assessment effort. In case of a joint submission, the amount could be divided by charging equally MAHs that have the obligation to conduct the PASS assuming that any further division between all MAHs that have taken part in the PASS could be arranged for by the MAHs themselves.

Pharmacovigilance referral

The concept of grouping was considered by respondents to the consultation more relevant in the case of pharmacovigilance referrals, but several respondents, notably the generics industry, request clarification about how the fee would be divided. In order to be connected to the assessment effort and bearing in mind the need of predictability and proportionality, a similar approach to the assessment of PSURs was taken, i.e. using the chargeable unit at the level of MAs (EV-codes) for a proportionate division among the MAHs involved..

ANNEX 5 – SMES ASPECTS OF THE ASSESSMENT

In the European Union overall, there are some 10 826[32] MAHs having at least one marketing authorisation of a medicinal product. The estimate on the proportion of SMEs is 90 %[33]. The micro-enterprises represent 33 % of the MAHs within the SMEs category[34].

As regards EV-codes and marketing authorisations (MA), the estimated values used in this impact assessment are given in Table 16 below. For the purposes of fee calculations in Annex 4, the percentages of EV codes (1.44 %) and MAs (1.67 %) held by SMEs were adjusted to 10 % due to the probable residual non-compliance in Article 57(2) database.

Table 16: Estimates of chargeable units - EV codes and MA, per category of MAH

Non-SMEs	EV codes	MAs	MAHs		
CAP	29951	9339			
Non-CAP	353444	278794			
Total	383395	288133	3293	30%	
SMEs	EV codes	MAs	MAHs	EV codes held by SME	MA held by SMEs
CAP	1034	823			
Non-CAP	4500	3992			
Total	5534	4815	247	1,44% (10%)*	1,67% (10%)*
- of which micro	1399	1231	82	25%	26%

Source: EMA, Art 57 database, situation as of February 2013
*adjusted figure

The proposed SME reductions are based on the comparisons of added values per employee as a possible measure of profitability of companies. Using this measure, the small and medium enterprises in the pharmaceutical sector are on average 40 % less profitable than non-SMEs, as indicated in Table 17 below. The micro-enterprises are 60 % less profitable per employee than the big pharmaceutical companies. Accordingly, it is assumed that the small and medium enterprises should be charged 60 % of the standard fee, whereas the micro-enterprises are assumed to be entirely exempted from the obligation to pay pharmacovigilance fees. The underlying reason for exempting the micro-enterprises is the fact that the already small number of EV-codes held by SMEs is further decreased by a factor of 4 in case of micro enterprises , which implies that the administration burden of collecting the fee would exceed the benefits from its collection. Furthermore, this is in line with the general EU policy to specifically exempt wherever possible micro-enterprises from EU legislation or introduce special regimes so as to minimise the regulatory burden on them[35].

[32] This figure represents an estimation of the number of individual MAHs in the EU as of February 2013 as registered in the EMA database (Art 57). A certain degree of non-compliance is posisble.
[33] The estimate is based on EMA figures as of February 2013. The number of non-SMEs in the CAP register amounts to 3293 MAHs. Projections of that figure would imply that ca. 70 % of MAHs are SMEs. However, Eurostat data (NACE C21-manufacture of basic pharmaceutical products and pharmaceutical preparations; 2009-2012) indicate that 90 % of pharmaceutical companies in the EU are SMEs and the latter figure was used in this impact assessment.
[34] This estimation is based on the proportion of micro-enterprises (82) of the total number of SMEs (247) as currently registered in the EMA SME Register.
[35] COM(2011) 803 final.

Table 17: Value added per employee and type of company

Type of enterprise	Value added / employee				
	2008	2009	2010	2011	2012
micro	64%	40%	40%	40%	41%
small	48%	45%	44%	43%	44%
medium	60%	66%	63%	62%	61%
SMEs	57%	61%	58%	57%	57%
Non-SMEs	100%	100%	100%	100%	100%

Calculations based on Eurostat SBS data

The impact on SMEs for all the options for fee collection is calculated in Annex 4. The calculations show that for the preferred option the increase in the standard flat fee due to reductions to SMEs would be only marginal. Furthermore, the administrative burden of collecting a small flat fee from micro-enterpriss would exceed the actual benefit of collecting such a fee. The number of invoices would be disproportionate to the amount charged to these companies. This, read in conjunction with the general EU policy on SMEs, leads to the conclusion that the most effective and efficient approach to SMEs seems to be the exemption/reduction of these companies. The SMEs overall contribution to pharmacovigilance activities through fees would thus be overall proportionate to their share of the market.

Further mitigating measures for SMEs

Incentive measures have been already introduced in the past in order to alleviate the burden on SMEs and soften the impact on smaller companies. All SMEs in pharmaceutical sector have already access to and can benefit from these measures. This is also the case for those companies that will be directly influenced by the pharmacovigilance activities of the EMA. Some measures are outlined below:

SME office

The SME office of the EMA provides information on companies with SME status that are registered with the European Medicines Agency. The office was created in consultation with SME stakeholders with the objectives (1) to facilitate and promote interaction, partnering and networking between SMEs; (2) to increase information available to SMEs and their stakeholders; (3) to provide a source of information for European Union (EU) institutions, agencies and Member States.

EVWEB

The EudraVigilance system provides a web based tool to allow for a manual safety and acknowledgement message creation as well as generation of medicinal product reports via a web interface, called EVWEB. It is specifically designed for SMEs and non-commercial sponsors, which do not have a fully compliant pharmacovigilance system and/or electronic transfer gateway in place. As such it provides the necessary tools to allow SMEs to perform secure electronic reporting to the EMA.

The companies are required to undertake and pass EudraVigilance training , which is held at the EMA every month and at various venues around the EEA. There is a fee reduction available to SMEs participating in these training sessions. Online materials are also available. Alternatively, SMEs may subcontract the electronic transmission of ADRs.

ANNEX 6 – PROVISIONS OF THE 2010 PHARMACOVIGILANCE LEGISLATION RELATING TO FEES

Article 67of the Regulation:

'The Agency's revenue shall consist of a contribution from the Union and fees paid by undertakings for obtaining and maintaining Union marketing authorisations and for other services provided by the Agency, or by the coordination group as regards the fulfilment of its tasks in accordance with Articles 107c, 107e, 107g, 107k and 107q of Directive 2001/83/EC.' (new Article 67(3))

'Activities relating to pharmacovigilance, to the operation of communications networks and to market surveillance shall be under the permanent control of the Management Board in order to guarantee the independence of the Agency. This shall not preclude the Agency from charging fees to marketing authorisation holders for performing these activities by the Agency on the condition that its independence is strictly guaranteed.' (new Article 67(4))

A similar wording to Article 67(2) above is included in the Directive 2010/84:

Article 105

"The management of funds intended for activities connected with pharmacovigilance, the operation of communication networks and market surveillance shall be under the permanent control of the national competent authorities in order to guarantee their independence in the performance of those pharmacovigilance activities.

The first paragraph shall not preclude the national competent authorities from charging fees to marketing authorisation holders for performing those activities by the national competent authorities on the condition that their independence in the performance of those pharmacovigilance activities is strictly guaranteed."

The following recitals of Regulation (EU) No 1235/2010 confirm that the legislator had the intention that fees will now become the major source of revenue for financing the pharmacovigilance activities of the EMA and the scientific assessment conducted by the Pharmacovigilance Risk Assessment Committee (PRAC) or the coordination group for human medicinal products (CMDh):

(13) In order to protect public health, the pharmacovigilance activities of the Agency should be adequately funded. It should be ensured that adequate funding is possible for pharmacovigilance activities by empowering the Agency to charge fees to marketing authorisation holders. However, the management of those collected funds should be under the permanent control of the Management Board in order to guarantee the independence of the Agency.

(14) To ensure the highest levels of expertise and the functioning of the Pharmacovigilance Risk Assessment Committee, rapporteurs providing assessments for Union pharmacovigilance

procedures, periodic safety update reports, post-authorisation safety study protocols and risk management systems should receive payment through the Agency.

(15) Therefore, the Agency should be empowered to charge fees in return for performing the activities of the coordination group within the Union system of pharmacovigilance, as provided for in Directive 2001/83/EC, and the rapporteurs within the coordination group should, in turn, be paid by the Agency.

Also an equivalent recital to number (13) of the Regulation cited above is included in the Directive 2010/84:

(30) In order to protect public health, the pharmacovigilance activities of national competent authorities should be adequately funded. It should be ensured that adequate funding is possible for pharmacovigilance activities by empowering the national competent authorities to charge fees to marketing authorisation holders. However, the management of those collected funds should be under the permanent control of the national competent authorities in order to guarantee their independence in the performance of those pharmacovigilance activities.

ANNEX 7 – ASSESSMENT CRITERIA AND THE IMPACT OF INDIVIDUAL OPTIONS

Stakeholder / criteria	Assessment			
	Option 1	Option 2	Option 3	Option 4
EMA / EC				
Balanced distribution of rapporteurship	Impossible to achieve	Neutral to positive (in all options, rapporteurs would be remunerated according to a fixed scale based on average estimated costs and workload per procedure)	Neutral to positive (in all options, rapporteurs would be remunerated according to a fixed scale based on average estimated costs and workload per procedure)	Neutral to positive (in all options, rapporteurs would be remunerated according to a fixed scale based on average estimated costs and workload per procedure)
Image / perception (reputation)	Perception of failure to act Loss of credibility	Although the annual fee revenue would be on average cost-based, individual fees could be perceived as non-cost-based in some cases.	Neutral with possible residual risk with regard to the flat fee.	Neutral with possible residual risk with regard to companies having to pay for activities that are not directly related to the service provided to them.
Employment (workload)	Impossible to measure	Depending on the mechanism of charging the fee, the effect on workload for EMA should not be significant. This is mainly because it is intended that	Depending on the mechanism of charging the flat fee component, the effect on workload for EMA should be moderate mainly because of the	The effect on the workload for EMA should be from moderate to significant, e.g. depending on the number of procedures occurring each year.

Stakeholder / criteria	Assessment			
	Option 1	Option 2	Option 3	Option 4
		the invoicing would be automated. The EMA estimates that administrative costs involved would be negligible.	intended automated invoicing (as under option 2). However, the effect on the workload for charging the procedural fee component could be from moderate to significant, e.g. depending on the number of procedures occurring each year.	
Simplification	Impossible to achieve	The level of simplification for EMA would depend on the mechanism of charging the fee. An automated invoicing would be an important simplification.	The level of simplification for EMA would depend on the mechanism of charging the flat fee. The automated invoicing for the flat fee component would be an important simplification. However, the invoicing of the procedural fee component cannot be fully automated. This option is therefore less simple than options 2 and 4	Yes: fees charged only per procedure. Although the invoicing of this fee cannot be fully automated, there are significantly fewer transactions and invoiced parties compared to options 2 and 3.
Clarity and transparency of the system	Impossible to achieve	Such a system could be clear but not entirely transparent.	More transparent than option 2 because the procedure-based fee	The elimination of the flat fee could lead to this option being perceived as

Stakeholder / criteria	Assessment			
	Option 1	Option 2	Option 3	Option 4
			component is paid only when the procedure occurs.	more transparent than option 3. This effect may be offset by the higher level of fees.
Efficiency / proportionality to tasks	Impossible to achieve	Efficiency would depend on the mechanism of charging the fee. Automated invoicing would contribute to efficiency. Proportionality would be achieved on a global level, but could be questionable on an individual level.	Efficiency would depend on the mechanism of charging the flat fee. Proportionality would be increased compared to option 2 in respect of the procedure-based fee component.	Depending on the mechanism of charging the flat fee, the elimination of such a flat fee could lead to more efficiency as compared to option 3.
Manageability of the system	Impossible to achieve	Depends on the mechanism of charging the fee. Automated invoicing would improve the manageability but this positive effect might be undermined by possible debt arrears.	Depends on the mechanism of charging the flat fee. Automated invoicing would improve the manageability of the flat fee component, however the invoicing of the procedure fee component cannot be fully automated. This option would be more complex to manage compared to	This option would be less complex compared to option 3. The complexity will depend largely on the number of procedures. Invoicing will not be completely automated but there will be fewer transactions and invoiced parties annually compared to option 2.

Stakeholder / criteria	Assessment			
	Option 1	Option 2	Option 3	Option 4
			options 2 and 4.	
Continuity of operation / service	Impossible to achieve	Depends on the mechanism of charging: rapporteurs would have to be paid irrespective whether invoiced fees are cashed. Furthermore, adjustment to the actual cost, i.e. for an increase in Referral activities, would be difficult to achieve on an yearly basis.	Payment to rapporteurs would be more easily linked to the procedure-based fees, even though this payment does not necessarily occur after the fee has been cashed.	Payment to rapporteurs would be more easily linked to the procedure-based fees, even though this payment does not necessarily occur after the fee has been cashed.
Sufficient funding	Impossible to achieve	This criterion would be met on an average annual level, but difficulties might arise if the volume of procedures rises significantly.	Both procedure-based and other activities would be funded in a timely manner (for other activities, the mechanism of charging the flat fee could have a bearing).	Procedure-based fees would fund the entire pharmacovigilance activities of EMA. Regularity of PSUR assessment would have a positive effect on the funding of non-procedure activities of EMA, but this positive effect might be undermined by lower activity levels for PASS and PhV Referrals.

Stakeholder / criteria	Assessment			
	Option 1	Option 2	Option 3	Option 4
Cost based fees	Impossible to achieve	Yes on annual level, not on individual level.	Yes for procedure-based fees. Flat fee: yes on annual level, not necessarily on individual level.	Less than option 3 due to distribution of the non-procedure activities costs to procedure-based fees.
Service based fees	Impossible to achieve	No: the fee would be disconnected from the actual provision of the service.	Yes for procedure-based fees. Flat fee: yes on annual level, not necessarily on individual level.	Less than option 3 due to distribution of the non-procedure activities cost to procedure-based fees.
Administrative burden / administrative costs	n.a.	Depends on the mechanism of charging. Automated invoicing would reduce the administrative burden and costs. The EMA estimates that administrative costs involved would be negligible.	Automated invoicing would reduce the administrative burden and costs for the flat fee component. As regards procedure-based fees, fully automated invoicing is not envisaged, however, the administrative burden will largely depend on the number of procedures and the number of transactions and invoiced parties involved in each procedure. Therefore, higher administrative	Fully automated invoicing is not envisaged, however, the administrative burden will largely depend on the number of procedures and number of MAHs and products involved in each procedure. Lower administrative burden compared to option 3.

Stakeholder / criteria	Assessment			
	Option 1	Option 2	Option 3	Option 4
			burden compared to option 2.	
Pharmaceutical industry (MAH)				
Cost based fees	Impossible to achieve	Individual fees might be perceived by some industry stakeholders as non-cost-based. This is the case in particular for MAHs that do not expect any (or very little) involvement in the EU procedures, even though they might benefit from the system.	Yes for procedure-based fees. Flat fee: yes on annual level, not necessarily on individual level.	Less than option 3 due to the distribution of the non-procedure activities cost to procedure-based fees leading to a risk to be perceived as unfair as companies not paying the fee during a given year could nevertheless benefit from the system.
Service based fees	Impossible to achieve	No: the fee would be disconnected from the actual provision of the service.	Yes for procedure-based fees. Flat fee: yes on annual level, not necessarily on individual level.	Yes, with distribution of the non-procedure activities cost to procedure-based fees. However, the fees under this option are less service-based than under option 3.
Proportionality of work / fee	Impossible to achieve	On an individual level, this criterion would be perceived as not met in all	Yes for procedure-based fees, as they are cost-based. Flat fee: yes on	Yes, with a proportionate distribution of the cost of non-procedure related

Stakeholder / criteria	Assessment			
	Option 1	Option 2	Option 3	Option 4
		cases (not all substances/products bear the same risk and / or require the same work).	annual level, not necessarily on individual level. Compared to options 2 and 4, this is, however, the most proportionate option.	activities. However, this is less proportionate than option 3, but more proportionate than option 2.
Transparency / clarity of the system	Impossible to achieve	The system would be perceived as clear but not fully transparent.	More transparent than option 2, as for the procedure-based fees, the fee is paid when the procedure occurs. Because of the flat fee, also companies that are not involved in the procedures would finance the non-procedure related pharmacovigilance costs.	The elimination of the flat fee could lead to this option being perceived as more transparent than option 3. However, the general EMA costs (i.e. not linked to procedures) would be distributed only amongst MAHs that participate in the EU procedures in a given year.
Fairness	Impossible to achieve	The system would not be perceived as fair by all MAHs, especially those whose products have a well-established safety profile and would thus normally be less involved in the EU procedures.	Fairer than option 2, save the flat fee that might still raise the same concern.	Yes, with a proportionate distribution of the cost of non-procedure related activities this could be considered acceptable. However, those MAHs that are not subject to any EU procedures would not contribute to the financing

Stakeholder / criteria	Assessment			
	Option 1	Option 2	Option 3	Option 4
				of the system. Therefore, this option would be considered less fair compared to option 3.
Non-duplication of fees at EU/ national level	n.a.	The activities for which EMA is charging and the corresponding costs should be clearly defined to enable the MAH to verify that they are not double-charged. However, compared to procedural fees, there is a higher risk of perception of duplicative charging. A single 'flat' fee would be less easy to take into account at national level when adjusting national fees.	This option presents the most detailed fee grid, which would facilitate comparison with national fees. The flat fee would cover PhV activities that are carried out only at the level of the EMA..	The level of procedure-based fees would be increased by the cost of non-procedure based activities. However, the content of procedures covered by such fees would be known, which would enable analysis in avoiding duplicative charging at national level.
Simplification / reduction of administrative burden	Impossible to achieve	Depending on the mechanism of charging, this criterion is likely to be fulfilled for MAH: one payment per year.	MAHs that are involved in procedures would have to pay both when a procedure occurs and on a yearly basis for the flat fee. However, MAHs that are	MAHs would only have to pay when a procedure occurs. This would thus be overall simpler than option 3.

Stakeholder / criteria	Assessment			
	Option 1	Option 2	Option 3	Option 4
			not involved in any procedures would only pay the flat fee.	
Predictability		Yes, a flat-fee would be predictable for MAHs (and EMA) regardless of the number of procedures a company would be involved in and irrespective of the mechanism of charging.	The fees for PhV referrals and for PASSes would be less predictable (compared to the flat fee) because the actual occurrence and the scope of such procedures are not known in advance. PSURs are more predictable due to the EURD list (as explained in Annex 1).	The fees for PhV referrals and for PASSes would be less predictable compared to PSURs because the actual occurrence and the scope of such procedures are less predictable. PSURs are more predictable.
NCA / MS				
Cost based fees	Impossible to achieve	The calculation of the fee would include the estimated average costs for NCAs rapporteurs but this link would not be visible at individual level. NCAs would be remunerated for their average estimated costs per evaluation procedure.	Yes: the amount of the procedure-based fees would be linked to the average cost of NCA rapporteurs.	Not entirely: the procedure-based fees would include an 'overhead' for the cost of non-procedure related activities.

Stakeholder / criteria	Assessment			
	Option 1	Option 2	Option 3	Option 4
Coverage of the NCA work / adequate remuneration of assessment work of rapporteurs	Impossible to achieve	Yes: all rapporteurs would be remunerated according to a fixed scale, based on average estimated cost and workload per procedure.	Yes: all rapporteurs would be remunerated according to a fixed scale, based on average estimated cost and workload per procedure.	Yes: all rapporteurs would be remunerated according to a fixed scale, based on average estimated cost and workload per procedure.
Expertise development, enhancement, sharing	n.a.	Neutral: all rapporteurs would be remunerated according to a fixed scale, based on average estimated cost and workload per procedure.	Neutral: all rapporteurs would be remunerated according to a fixed scale, based on average estimated cost and workload per procedure.	Neutral: all rapporteurs would be remunerated according to a fixed scale, based on average estimated cost and workload per procedure.

ANNEX 8 – WIDER CONTEXT OF THE INITIATIVE

European Medicines Agency (EMA)

The EMA operates through a network of NCAs and coordinates the scientific resources made available by them, thereby ensuring the evaluation and supervision of medicinal products. The EMA is an EU body with its own legal personality and is one of the few EU Agencies which are fee-earning. The revenue of the EMA consists of an EU contribution (approximately 20%) and fees from industry (appr. 80%) charged to MAHs for obtaining and maintaining EU marketing authorisations.

At the start of year N-1, EMA prepares a preliminary draft budget which is adopted by its Management Board usually at its March meeting of N-1. The final budget of EMA is prepared at the end of year N-1 and it takes account of the budget of the European Union, as proposed for adoption by the Budgetary Authority. After the adoption of the budget and the establishment plan for year N by the EMA Management Board, a copy is sent to the European Parliament. The annual budget is published on the external website of the EMA and a summary version is published in the Official Journal of the European Union.

The EMA budget for 2012 was €223,5 million of which €183 million stems from fees and €39 million from EU contributions. Over the last 10 years the proportion of the revenue from fees has increased whereas the proportion from the EU contribution has decreased.

Marketing Authorisation procedures

Given that it is proposed that EMA could also charge pharmacovigilance fees for non-centrally authorised medicinal products, a brief description of the system of authorisation of medicinal products in the EU is given below.

Medicinal products authorised by the Commission in accordance with the procedure under Regulation No 726/2004[36] (the so-called “centralised procedure”) are referred to as 'centrally authorised products' ('CAPs'). A marketing authorisation (MA) can also be issued by an 'NCA' for its own territory (pure national marketing authorisation). As regards MAs in several Member States (MSs), two authorisation procedures exist:
(i) the mutual recognition procedure ('MRP') where a medicinal product is first authorised in one MS under the national procedure, and in the case where subsequent applications for MAs are filed in other MS, the latter agree to recognise the validity of the first MA; and
(ii) the decentralised procedure ('DCP') where the MA applications are submitted simultaneously in different MS and for which one MS acts as reference MS (carrying out the scientific evaluation).
Products authorised by the NCAs under any of the latter three procedures (i.e. purely national authorisations and authorisations under the MRP or DRP) are hereinafter referred to jointly as 'non-centrally authorised products' ('non-CAPs'). After the granting of the MA, the MAH will benefit from data exclusivity for a period of at least 8 years (during which generics cannot enter the market). This data exclusivity applies in parallel with provisions on patents. These rules are intended as incentives to originator companies for innovation.

[36] 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, OJ L 136, 30.4.2004

The EMA is responsible for the evaluation, authorisation and supervision of medicinal product for human and veterinary use in accordance with the procedures laid down in the Regulation. The EMA currently also has a role for non-CAPs in the context of referrals, however, such referrals are not subject to fees except if the referral is triggered by the MAH (which so far has not happened). A referral is a procedure used to resolve issues such as concerns over the safety of a medicine or a class of medicines or in cases of disagreements among Member States on the use of the medicine. The medicine, or the class of medicines, is 'referred' to EMA, so that it can make a recommendation for a harmonised position across the European Union which often leads to the Commission adopting a decision addressed to the Member States, reflecting the measures to take to implement the recommendation. A referral can normally be triggered by the Commission, the Member States or the MAH. While there are different types of referrals, this IA (and any possible legal proposal that derives from it) only deals with **pharmacovigilance referrals** and hence fees for pharmacovigilance referrals, as only they are within the scope of the 2010 pharmacovigilance legislation. Pharmacovigilance referrals are typically triggered by the MS or the Commission.

2010 Pharmacovigilance legislation

A major revision of the EU legislation on pharmacovigilance was introduced in 2010 through the adoption of

- Regulation (EU) No 1235/2010 of the European Parliament and of the Council amending, as regards pharmacovigilance of medicinal products for human use, Regulation No 726/2004 and
- Directive 2010/84/EU of the European Parliament and of the Council amending, as regards pharmacovigilance, Directive 2001/83/EC.

The new legislation became applicable in July 2012 The changes affect CAPs and non-CAPs. Given that the 2010 pharmacovigilance legislation provides a greater role for EMA in the area of pharmacovigilance in general, i.e. irrespective of how the medicinal products have been authorised (therefore including both nationally and centrally authorised products), EMA will for the first time be able to charge fees also for nationally authorised products. Many NCAs currently charge the MAHs for pharmacovigilance activities, and hence there is also a need to ensure that MAHs are not charged twice for the same work. Therefore, the fees of EMA should be transparent in order for companies to be able to identify what pharmacovigilance activities the new fees would correspond to. It should also be borne in mind that while the 2010 Pharmacovigilance legislation lays down certain obligations on the MAHs, the activities of the regulatory authorities in the area of pharmacovigilance (i.e. detection of safety signals, assessment of these signals and regulatory follow-up) constitute a service to the MAHs.

The Commission's proposal of 10 December 2008 to amend the pharmacovigilance legislation was accompanied by a Financial Statement[37] according to which all costs related to activities resulting from the legislative proposal are to be recuperated through fees.

Fees Regulation and Implementing Rules

Fees are currently charged by the EMA in accordance with Council Regulation (EC) No 297/95 (Fees Regulation)[38]. The Fees Regulation sets out fees for CAPs and in the case of

[37] http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=COM:2008:0664:FIN:en:PDF.
[38] OJ L 35, 15.2.1995 p.1

some referrals initiated by the MAH also for non-CAPs[39]. The Fees Regulation was last amended in 2005. For the application of the Fees Regulation, there are Implementing Rules adopted by the Management Board of EMA.
The existing pharmaceutical legislation provides for various fee incentives for SMEs for CAPs.

Remuneration of the MS rapporteurs

The legislation and the Implementing Rules of the current Fees Regulation provide, *inter alia*, that the NCAs acting as rapporteurs or co-rapporteurs, i.e. carrying out the evaluation of medicinal products and the subsequent follow-up, are remunerated by the EMA for their work. It may be noted that there is currently also some work carried out by the rapporteurs/co-rapporteurs for which they are not remunerated. For the evaluation of an initial marketing authorisation under the centralised procedure (for which the current fee is approximately 270.000€), the rapporteurs/co-rapporteurs receive 50% of the fee charged by EMA. The European Court of Auditors, in its annual reports on the EMA, has repeatedly been criticising that these payments to the MS are not cost-based. Recently, also the European Parliament has raised criticism on this point in the context of the discharge procedure. Hence, the EMA has been requested to report to the EP on progress made in this area by May 2013. This is currently in the competence of the Management Board, as the level of remuneration of MS is laid down in the Implementing Rules of the existing Fees regulation.

Legal base to charge fees for pharmacovigilance activities under the 2010 Pharmacovigilance legislation

Whereas the previous (2004) wording of Article 67(4) of the Regulation provided that pharmacovigilance activities are to be publicly funded, the revised Regulation (as amended by the 2010 pharmacovigilance legislation) provides that industry is to be charged fees by EMA for the conduct of pharmacovigilance activities. In order to enable EMA to charge fees for pharmacovigilance, there is a need for a legal instrument.

[39] In practice, however, this fee is never applied.

ANNEX 9 – ASSIGNING IMPORTANCE TO THE ASSESSMENT CRITERIA

Analytical hierarchy process technique was used in order to assign weights to each of the four criteria used in the assessment in order to reflect and formalize its relative importance. As a first step, a pairwise comparison of the criteria was made through a series of judgments in order to construct a ratio scale. The comparison values are outlined in Table 3 and were defined as follows:

1 Both criteria are of equal importance
2 Criterion A is slightly more important than criterion B
3 Criterion A is strongly more important than criterion B
4 Criterion A is very strongly more important than criterion B
5 Criterion A is absolutely more important than criterion B

Table 3: Comparison values

B / A	transparency	stability / predictability	simplicity	fairness / proportionality
Transparency	1	3	4	1/2
stability / predictability	1/3	1	2	1/3
Simplicity	1/4	1/2	1	1/4
fairness / proportionality	2	3	4	1

A simple calculation was made in Table 4 to determine the overall weight that we assign to each criterion and that will be subsequently used for making the decision on preferred option. This weight is between 0 and 1 and the total weight adds up to 1. The overall weighting column establishes priorities among the criteria used. The results suggest that 45 % of the objective weight is on fairness and proportionality, 32 % on transparency, 14 % on stability and predictability and 9 % on simplicity.

Table 4: Relative weighting of criteria

	transparency	stability / predictability	simplicity	fairness / proportionality	**Overall Weighting**
transparency	0,279	0,400	0,364	0,240	**32%**
stability / predictability	0,093	0,133	0,182	0,160	**14%**
simplicity	0,070	0,067	0,091	0,120	**9%**
fairness / proportionality	0,558	0,400	0,364	0,480	**45%**
	1	1	1	1	**100%**