AESGP position paper
on the European Commission's Consultation relative to the Introduction of Fees to be Charged by the EMA for Pharmacovigilance

AESGP represents the manufacturers of non-prescription medicines of chemical, herbal or homeopathic origin at European level. It counts 29 national associations and 25 associate members.

AESGP appreciates being given the opportunity to take part in this consultation, which is of high importance for our sector.

General remarks:

- The Concept Paper departs from the legislator's original intention to strengthen and rationalise the existing pharmacovigilance requirements. The impact assessment was anticipating important potential annual savings for the pharmaceutical industry (€244,997,456, i.e. €145,175,510 net savings after deduction of the potential annual cost increase – cf. table below).

Table 12 Quantification of total economic impacts on the industry

Options	Potential annual cost increase	Potential annual savings
Company Pharmacovigilance System Master File		€ 85,900,000
Clear legal basis for risk management plans	€ 89,225,945	
ADR Reporting simplification		€ 77,143,723
Literature screening by the EMEA		€ 10,000,000
Removal of routine requirement for PSUR+Worksharing		€ 71,953,732
Increase in fees payable to EMEA	€ 10,596,000	
Total	€ 99,821,945	**€ 244,997,456**

Source: Pharmacovigilance Impact Assessment (Page 55) - http://ec.europa.eu/health/files/pharmacos/pharmpack_12_2008/pharmacovigilance-ia-vol1_en.pdf

The impact assessment's forecasted increase in fees payable to the EMA was €10,596,000 annually. However a rough estimate of the potential annual cost increase for the industry based on the proposed fees already results in a much higher figure. Some companies have indicated to us that their individual cost burden would already be higher than the estimated fee increase for the entire industry. This illustrates that the envisaged fee levels are out of proportion. In addition, due to these fees, it can also be anticipated that a number of well-known products would disappear from the market as the actual pharmacovigilance costs would surpass the revenues generated.

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- We are particularly concerned about the fee levels proposed for activities such as PSURs, referrals and service. The proposed levels exceed by far those proposed in the annex of the Commission's 2008 proposals. Whilst we understand that workload has been added to the original proposals, this does not justify such an increase, in particular for non-prescription medicines which usually have a well-known safety profile and a long-standing safety experience. Most non-prescription medicines were placed on the market decades ago, and adverse drug reactions (ADRs) are very rare and only in exceptional cases serious. We therefore call on the Commission to reconsider the proposed fees taking into account the proportionality principle.

- Contrary to a marketing authorisation application or a scientific advice, pharmacovigilance provisions are an obligation for pharmaceutical companies with medicinal products on the market. As Recital 2 of the Pharmacovigilance Regulation states that "*pharmacovigilance rules are necessary for the protection of public health in order to prevent, detect and assess adverse drug reactions to medicinal products placed on the Union market, […]*", the total or predominant reliance on private funding for pharmacovigilance activities seems contrary to this objective. Moreover, pharmacovigilance is a sovereign responsibility, and the costs are not supposed to be completely financed by fees.

- *No double charging for companies*: A key objective described in the Roadmap concerning the legislative proposal on a Regulation/Directive amending the Regulation of the EMA on Fees was to "*avoid that companies are charged twice (by EMA and the Member States) for the same work*". It should indeed be guaranteed that this principle applies in practice as overlaps are possible in the case of nationally authorised medicines. These will indeed appear in the Extended EudraVigilance Medicinal Product Dictionary (XEVMPD) – and may hence be charged the annual service fee – without necessarily benefiting from the EMA services if they are only marketed in one Member State, as they will continue to be charged at national level. In addition, medicines marketed only at local level (in one Member State) are typically marketed by smaller companies (SMEs) for which paying double fees would be particularly unfair and contrary to the aim of the legislation.

- *Proportionality*: The principle of proportionality between the amount (level) of the fees and the nature of the work/tasks to be carried out by the EMA must be factored in when fees are proposed, e.g. for the assessment of a PSUR for a well-known substance. The actual workload for the assessors is considerably lower with regard to PSURs for longstanding and well-known products than for new chemical entities.

- *Pharmacovigilance Service fee*: It is unclear what the service fee will exactly cover. In addition, the concept paper states that "*the pharmacovigilance legislation will become applicable in July 2012 and therefore it is urgent to enable the EMA to charge fees for the fulfilment of its pharmacovigilance tasks*"… This sentence seems at odds with the reality as a number of pharmacovigilance services were not prioritised and will not come to life before 2015-2016, including a functioning EudraVigilance tool for ICSRs, a functional PSUR repository, single assessment process at full capacity, literature screening service and, in general, access to the EudraVigilance for the pharmaceutical industry.

- *Transparency-Predictability*: In the case of the grouping scenario, it is not clear in advance how high the fee level would be in the end. Example: If there is a referral of a well-known active, the Marketing Authorisation Holder (MAH) cannot know how many other MAHs will be part of the referral.

- The revision of the fees for the pharmacovigilance system in isolation is difficult without reviewing the whole fee system given that a number of new pharmacovigilance measures are likely to engender variations.

1. FEE FOR ASSESSMENTS OF PERIODIC SAFETY UPDATE REPORTS

Consultation item n°1: Do you agree with the proposed fee for single assessment of PSURs? If not, please explain and/or suggest alternative.

The proposed fees for PSURs completely disregard the proportionality concept, which was one of the main pillars of the revision of the new pharmacovigilance legislation.

We do not agree with the proposed fee for single assessment of PSURs, which is really too high for non-prescription medicines with usually limited post-marketing information to review.

Although benefiting in principle from the general waiver to submit PSURs due to the legal basis of the marketing authorisation, uncertainty remains over the way this provision will be interpreted by Member States: a strict application of the legal basis (scrupulously following the legal basis) could mean that PSURs will remain compulsory for many non-prescription medicines manufacturers. On the other hand, a more pragmatic interpretation of the waiver to include all homeopathic medicines and old medicines containing well-known substances authorised on the basis of a full marketing authorisation application (before bibliographic applications became a possibility) would mean that overall most companies in our sector would not have to submit PSURs. Given that the final content of the final URD list still needs to be decided, this may have an important impact on this matter.

For many well-established medicines which have been on the market for a long period of time, the number of individual case safety reports received per year is small compared to a new chemical entity. PSURs of well-known products contain data (predominantly literature and regulatory reports), with few actual case reports and very little 'new' data. Therefore the risk-benefit analysis is relatively simple. A PSUR for a new(er) product could contain many new data, and would necessarily involve more in-depth analysis. Fees of up to €80,300 are therefore completely disproportionate in light of the workload involved in the assessment of a PSUR for a well-established medicinal product. Due to the amount proposed, it can easily be foreseen that medicinal products with yearly sales below €80,000 would disappear from the market. This is even more out of proportion for herbal or homeopathic non-prescription medicines.

Seven EU countries have introduced PSUR fees ranging from €100 to €4,400. All of them have a sliding fee system taking into account the role of the country (RMS or CMS) or the number of years the product has been on the market, the type of product, etc. If we take the example of Austria, the highest fee is €3,600 in those cases where Austria is the Reference Member State in a mutual recognition or decentralised procedure, while the fee amounts to €500 when Austria is the Concerned Member State. For homeopathic medicines, the fee amounts to €100. In Germany the fee decreases when a product has been on the market for more than 10 years.

In addition (see page 56 of the Annex), calculation details of the Legislative Financial Statement appended to the Commission proposal for a Directive on pharmacovigilance[1] was foreseeing a fee of €6,100 per PSUR. This was a reasonable approach, and we wonder what triggered the more than ten-fold increase leading to the currently proposed fees.

The cascading fee effect should also be taken into account. The legislation (Recital 25) indeed states that *"any measures as regards the maintenance, variation, suspension or revocation of the MA resulting from a single PSUR assessment should be adopted through a Union procedure leading to a harmonised result. In other words, certain PSUR assessments would be followed by a referral procedure and possibly then by variations having to be submitted for non-CAPs in Member States where the product is authorised…"*. Under the currently proposed fees this could amount to an astronomical sum.

We would also like to request that consideration be given to the possibility of 'spreading' the payments over the PSUR period, rather than requiring the fees being paid as a lump sum.

In any case, the PSUR fees should be lowered and be based on / adapted to the expected level of work involved for a non-prescription medicine.

Consultation item n°2: Do you consider relevant the concept of grouping as proposed? If not, please explain and/or suggest alternative.

With regard to the concept of grouping, which in theory would reduce fees per Marketing Authorisation Holder (MAH), this is unlikely to work in practice and hence to generate the anticipated savings. We therefore do not believe that a fee calculation can be based on a considerable level of "grouping".

Whilst grouping could be relevant for marketing authorisation holders belonging to the same legal entity, it is not workable for marketing authorisations belonging to different legal entities/companies.

[1] http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=COM:2008:0665:FIN:en:PDF

A pilot on the preparation of a common PSUR for a well-established medicine was recently carried out in the United Kingdom. This showed that there were differences in data sets (including formats), concerns over sharing confidential information, and protracted discussions concerning the report's conclusions. The outcome of the pilot study was that whilst it is theoretically possible to prepare a common PSUR, this was not practicable. If it is not practical to produce a common PSUR by a small number of companies operating in the same country, these impracticalities can only be multiplied in case a common PSUR was to be attempted across several countries and a large number of Marketing Authorisation Holders.

Rather than limiting the fees per MAH through grouping, we think that a considerable lowering of the PSURs fees would be a more effective and fair solution.

2. FEE FOR ASSESSMENT OF POST-AUTHORISATION SAFETY STUDIES (PASSES)

Consultation item n°3: Do you agree with the proposed fee for the assessment of PASSes? If not, please explain and/or suggest alternative.

The proposed fees are again too high and from our perspective not justified. For the sake of proportionality, we would suggest making a distinction in the fees according to the novelty of the medicinal product and the complexity of the PASS.

We would also propose having three different fees per PRAC activity:

- PASS protocol assessment
- PASS protocol amendment assessment, if any
- PASS report assessment.

The MAH may decide to withdraw the medicinal product without completing the PASS. In that case no report would be generated for the PRAC to assess.

We would also suggest differentiating between a PASS voluntarily being developed by the MAH(s) and submitted to the PRAC for assessment and the PRAC developing the PASS protocol and imposing it on the MAH(s). Fees are only justified in the first case and not in the second.

Also, we propose that any activity resulting from the PASS core safety report assessment be free of charge. Depending on the type of activity needed (e.g. type II variation, RMP update etc.), these could then result in separate fees. The clinical trial application (CTA) to the Member State(s) participating in the PASS should follow a "fast-track"/simplified evaluation process. A reduction of the usual CTA fees is suggested given that the core PASS protocol evaluation has already been carried out by the PRAC.

In page 56 of the Annex (details of calculation of the Legislative Financial Statement appended to the Commission proposal for a Directive on pharmacovigilance), a fee of €6,100 per PASS was foreseen. We wonder what triggered the thirteen-fold multiplication leading to the cap fee currently proposed.

Consultation item n°4: Do you consider relevant the concept of grouping as proposed? If not, please explain and/or suggest alternative.

In general, we have doubts that the process of grouping would work. Fees should not be based on this concept but be reduced and calculated for each product. Furthermore, grouping may only be relevant for marketing authorisations belonging to the same company/legal entity but not for marketing authorisations belonging to different companies/legal entities.

3. Fee for Assessment of Pharmacovigilance Referrals

Consultation item n°5: Do you agree with the proposed fee for the assessment of pharmacovigilance referrals? If not, please explain and/or suggest alternative.

For reasons similar to those mentioned for PSURs, a fee ranging from €80,300 to €267,400 is inappropriately high. As per the comments on PSURs, the data available for well-established medicinal products are very likely to be limited (cf. the recent experience with pholcodine).

Currently, no fees are payable to the Agency for arbitrations and referrals under Articles 29, 30, 31 and 35 of Directive 2001/83/EC or Article 5(3) of Regulation (EC) No 726/2004 (human medicines) triggered by the Commission or Member States. We wonder why fees – especially of this level – should be paid under the new legislation.

The Annex to the Commission proposal, in page 56, foresaw a fee of €72,800 per referral. We wonder what triggered the four-fold increase leading to the cap fee currently proposed.

Whereas no Type II variation is foreseen for centrally authorised medicines (CAPs) to implement a labelling change following a pharmacovigilance referral, multiple fees will have to be paid for non-CAPs, e.g. for adding a contraindication:

- 1 x €80,300 for a pharmacovigilance referral (mandates new contraindications);
- X times the Type II variation fee for non-CAPs in concerned Member States (amend local labelling).

The question arises whether such cascading fees can be avoided to reduce the immense administrative and financial burden for industry to an appropriate level.

As Commissioner Dalli pointed out at the AESGP Annual Meeting in June 2012, PRAC-requested pharmacovigilance referrals should be rare and occur only where there are significant safety concerns. Indeed the above-mentioned Annex estimated the number of referrals to be approximately 20 per year. Based on this estimation, the proposed fee would generate an income for the EMA of between €1.6 million and €5.3 million.

Funding the safety referrals solely through private fees is undesirable as the EMA could be challenged over the independence of its safety decisions in light of its total reliance on industry fees. The Agency could be particularly open to scrutiny by the media and other stakeholders. It would therefore be preferable for the safety referrals to be partly or completely funded by public funds. Referral fees for industry should be abandoned or at least be considerably lowered.

Consultation item n°6: Do you consider relevant the concept of grouping as proposed? If not, please explain and/or suggest alternative.

As explained above, it is doubtful that the concept of grouping will work in general, and in particular under the tight timeline imposed by the new urgent union referral (60 days without clock stop). Rather than limiting the fee per MAH through grouping, we think that abandoning/ lowering the referral fees would be a more efficient and fair solution. If this is done, it would be important to clarify that the usual definition of 'same marketing authorisation holder' is being applied. Otherwise, separate fees could be required for each affiliate company.

4. PHARMACOVIGILANCE SERVICE FEE

Consultation item n°7: Do you agree with the proposed pharmacovigilance service fee? If not, please explain and/or suggest alternative

There has so far been a wide agreement that fees are linked to clearly identifiable service(s) provided to the industry. This is not the case for the pharmacovigilance service fee. All authorised medicinal products listed under Article 57(2) would have to pay the (annual) pharmacovigilance service fee, including those authorised purely at national level.

The submission of information on medicinal products under Article 57(2) of the Regulation is not done voluntarily by the MAHs. The administrative burden is extremely high for companies with many marketing authorisations, and the personnel and software costs to carry out this work are also high. Having to pay an extra fee is therefore not acceptable.

It is argued that the EMA provides literature monitoring, signal detection, monitoring of the effectiveness of public health measures, operation of the EudraVigilance database and the PSUR repository, etc. However, it was also made clear by the EMA that literature monitoring will only be performed for selected substances and in selected journals, and that the MAH's legal obligation to monitor the scientific literature and to process literature reports on adverse drug reactions will remain unchanged. Therefore, literature monitoring by the EMA does not shift any task or responsibility from the MAH to the EMA and can therefore not be regarded as a service.

The same applies to the future work the EMA will undertake on signal detection. The final responsibility for signal detection and evaluation remains with the MAH; therefore the EMA's activities do not shift any task or responsibility from the MAH to the EMA and, as a consequence, cannot be regarded as a service.

Monitoring of the effectiveness of public health measures and operating the EudraVigilance database and the PSUR repository cannot be regarded as a service to the MAH either but should rather be seen as a requirement for the Agency to fulfil its legal tasks.

No fee should be charged at all for this general service as it is in reality a public health service and should be funded by Community resources.

5. SMEs

Consultation item n°8: Do you agree with the proposed approach for fee reductions for SMEs as regards the pharmacovigilance procedures at EU level? If not, please explain why and provide suggestion how this could be improved.
Consultation item n°9: Do you agree with the proposed approach with regard to the pharmacovigilance service fee for SMEs.

We believe that fees for all companies should be considerably lowered. By that, a specific provision for SMEs would not be necessary.

Consultation item n°10: What other aspects would like to raise? Do you have additional comments?

We really would like to recall the original intention of the Commission's proposal: Improve safety of medicines by reducing unnecessary administrative burden and lowering costs. The Concept Paper does not reflect the intentions of the European Commission as expressed in 2008 and embedded in the new legal provisions.

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