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INTRODUCTION OF FEES TO BE CHARGED BY THE EMA FOR PHARMACOVIGILANCE

CONCEPT PAPER SUBMITTED FOR PUBLIC CONSULTATION

Comments of the European Confederation of Pharmaceutical Entrepreneurs (EUCOPE)

The European Confederation of Pharmaceutical Entrepreneurs (EUCOPE, www.eucope.org) represents via the member associations (the German Pharmaceutical Industry Association (BPI), the Ethical Medicines Industry Group (EMIG) of the UK, the German Biotech association BioDeutschland as well as the Swedish associations of mid-sized innovative companies IML and SwedenBIO), more than 900 mid-sized innovative member companies, many of them SMEs. In addition, many innovative companies from Sweden, UK, France, Bulgaria, Italy, Greece, Germany, the Netherlands and Austria are represented on the board of the association.

EUCOPE highly appreciates the opportunity to review and comment on the above mentioned Consultation paper. Please find some General Findings (I) and comments on the specific Consultation Items (II) below.

I. General findings

EUCOPE welcomes that the Commission takes into account the limited resources of SMEs and that the proposal foresees a fee reduction for such companies. However, we see need for amendments regarding the following aspects:

- transparent calculation of fees reflecting the actual workload for EMA (Consultation items No. 1, 3, 5, 7)
- fees should reflect the size of the market of a product and patient exposure (Consultation items No. 5, 7)
- only tasks for which EMA bears the final responsibility should be considered as services and thus be charged (Consultation item No. 7)

EUCOPE welcomes the principles set out in section 2.3 of the concept paper:

a) Proportionality between the amount (level) of the fees and the nature of the work/tasks actually carried out by EMA as well as the regulatory network (i.e. EMA and the NCAs) and maintaining consistency between fees for existing, comparable tasks/work across various procedures.

b) Transparency in order for marketing authorisation holders ('MAHs') to know to what tasks the fee corresponds to and to avoid that they are charged twice (by EMA and the Member States) for the same work.

c) Equal treatment of MAHs, except for justified reasons (e.g. SMEs).

d) Minimum additional administrative complexity of the fee structure by avoiding the introduction of additional fee levels.

Council Regulation (EC) No 297/95 on fees payable to the European Agency for the Evaluation of Medicinal Products[1] sets out the rule that "the calculation of the amount of the fees charged by the Agency must be based on the principle of the service actually provided".

In order to fulfill these principles - especially regarding the proportionality and equal treatment - we see need for changes and clarifications.

The proposal should explain the basis of the calculation, for example the reason for a thirteen fold increase in comparison with the 2008 Financial Statement[2] for a specific assessment for which the nature of the task carried out by EMA has not changed. The 2008 Financial Statement provides insight on the calculated workload at EMA, e.g. for the assessment of Periodic Safety Update Reports (1000 PSURs/year at 6.100 EUR). The proposal does not explain the amount of 80.300 EUR for a single PSUR assessment.

Furthermore, the question whether a fee is proportionate, e.g. the maximum fee of 80.300 EUR for a PSUR assessment, is linked with the question of how this fee will be divided between several MAHs. Concerning the equal treatment of MAHs and staying with the PSUR example, it needs to be noted that a fee of 80.300 EUR is payable irrespective of the workload and effort that the connected assessment procedure involves at the level of the Agency or the CMDh – quite obviously, this will lead to inequalities. MAHs acting on national or regional level are burdened above average.

The fee spectrum should furthermore give stronger consideration to purely national marketing authorizations. The current fees would make manufacturing of such pharmaceuticals uneconomical. This would affect most strongly existing original products with known active substances since the PSUR exemption in Art. 107b (3) of Directive 2001/83/EC as amended for generics and well-established use does not apply. They frequently fall under the PSUR requirement. Authorized homeopathic or herbal medicines, for which PSURs need to be submitted, are affected for the same reasons, too. This is also true for ophthalmic medicinal products where

[1] http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CONSLEG:1995R0297:20120401:EN:PDF.
[2] http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=COM:2008:0665:FIN:en:PDF and http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=COM:2008:0664:FIN:en:PDF.

due to the specificity of the products and although the medicinal product contains a generic or well-established active substance hybrid marketing authorization applications are asked for by the relevant competent authorities leading to the situation that the PSUR exemptions of Art. 107b (3) of Directive 2001/83/EC as amended do not apply.

Also a number of products have very specific combinations of active ingredients where the possibility to lower the costs of up to 80.300 EUR per PSUR by dividing them amongst the concerned marketing authorization holders does not seem feasible.

Apart from that there should be an exemption for all pharmacovigilance fees for orphan drugs which – given their nature – are intended for a small patient population only. These services should be covered by the annual fee and variation fees.

II. Response on specific Consultation Items

1. **Consultation Item No. 1: Do you agree with the proposed fee for single assessment of PSURs? If not, please explain and /or suggest alternative.**

   EUCOPE considers bench-marking the fees on a Type II variation EU-wide at 80.300 EUR as not differentiated enough. Not all products are approved in all Member States (MS) of the EU, and hence the commercial benefits are not EU-wide. Furthermore, the fees should reflect that for some products, e.g. homeopathics, the efforts of the evaluation are lower. At the same time, fees should be set for an 'average' evaluation as well as clear conditions and criteria for cases where higher fees are charged. The calculation of fees must be transparent and comprehensible.

   EUCOPE considers charging a fee per territory as appropriate. This fee could be an average of the current national fees for PSURs across the EU.

	national	CMS	RMS	New proposal EMA/Commission
	EUR	EUR	EUR	EUR
Austria	500	500	3.600	-
Belgium	1.177,04	1.147m04	2.272,57	-
Denmark	873	873	873	-
Germany	650 – 1.300	650 – 1,300	1.300 – 4.400	-
Iceland	1.630,30	98,88	2.379,21	-
Latvia	1.432	1.432	1.432	-
Lithuania	212	138	971	-
Slovenia	1.500	250	11.750	-
Spain	371,46 – 2.272,48	371,46 – 2.272,48	371,46 – 2.272,48	-
Total	**8.345,80 – 10.896,82**	**5.460,38 – 6.011,40**	**24.949,24 – 25.950,26**	**80.300 (40.150 for the first 2 years)**

   These numbers correspond also to the Commission's proposal in the 2008 Financial Statement.

Art. 107e of Directive 2001/83/EC foresees that PSUR assessments shall be performed – depending on the question whether a centralized marketing authorization is impacted at active substance level – either at coordination group level (CMDh) or at the Pharmacovigilance Risk Assessment Committee (PRAC). We understand the current proposal as follows: the fee for the implementation of PSUR assessments covers all costs, irrespective of whether the procedure is performed at the CMDh or the PRAC level and that no fees are charged independently by the CMDh. If this is not correct, with the low cost and effort involved at the Agency in cases where the PRAC does not perform the PSUR assessment, a considerably reduced fee should be charged: because then the PRAC activities would be limited to the activities mentioned in Art. 107e (3) of Directive 2001/83/EC as amended.

2. **Consultation Item No. 2: Do you consider relevant the concept of grouping as proposed? If not, please explain and /or suggest alternative.**

The concept of grouping is welcomed in principle. However, EUCOPE considers the grouping as proposed not feasible from a practical point of view given the competition between the MAHs involved in the process. Furthermore, it would have to be ensured that MAHs are aware of other MAHs using the same molecule and it would have to be clarified who writes the PSUR. The proposal as well as the respective Q&A document[3] whether grouping is to be understood as meaning that if several Marketing Authorization Holders submit one single PSUR together (because their products contain the same active substance or the same combination of active substances) whereby each of them would be charged an equal share of the entire applicable fee or whether several Marketing Authorization Holders submitt each a PSUR independently. Surely in the latter case the amount of 80.300 EUR would not be charged by EMA.

EUCOPE also sees need for clarification how to ensure that confidentiality on commercially sensitive information in the case of grouping is maintained.

In this regard, it would be helpful if the Commission could clarify in which cases different MAHs can join to file a single PSUR and hence reduce the costs. Is this possible for all cases where different marketing authorizations contain the same active substance even if the medicinal products in question were manufactured at different sites? As far as the PSUR normally partly contains product specific issues a grouping might be limited, in fact leading to a situation that there may be some “generic” parts of a PSUR that can be prepared together by different MAH while other parts have to be prepared separately by the different MAH. Will it be possible to group in this scenario even if parts of a PSUR that are specific for the different medicinal products in question (like e. g. the sales volumes) are differing?

If grouping would be understood also as cases where the submission is grouped between MAHs of the same corporate group, the idea of a fee reduction would be supported. There

[3] http://ec.europa.eu/health/files/pharmacovigilance/2012-07-09_qa_en.pdf.

is no additional workload in the assessment of the PSUR irrespective of the number of MAHs involved (one set of data from one PV system, collected and evaluated at one single point under global SOPs and under the supervision of one EU QPPV). In such cases, the proposed administrative fee of 500 EUR for each additional MAH in a group would not be justified.

3. **Consultation Item No. 3: Do you agree with the proposed fee for the assessment of PASSes? If not, please explain and/or suggest alternative.**

   EUCOPE does not agree with the proposed fee for the assessment of PASSes because the basis for the calculation is unclear. The fee has to correspond to the workload in a transparent manner. Compared to the 2008 Financial Statement the amount in the current proposal has increased by factor 13 whereas the task conducted by EMA remains the same. Furthermore, the proportionality of the proposed fee of 80.300 EUR has to be taken into account regarding certain products (e.g. homeopathics, the proposed fee is 20-fold higher than a new national marketing authorization).

4. **Consultation Item No. 4: Do you consider relevant the concept of grouping as proposed? If not, please explain and/or suggest alternative.**

   EUCOPE sees the same difficulties as described for the PSURs (see Consultation item no.2).

5. **Consultation Item No. 5: Do you agree with the proposed fee for the assessment of pharmacovigilance referrals? If not, please explain and/or suggest alternative.**

   EUCOPE considers that there should be no fee for pharmacovigilance referrals following the procedure under Art. 107i, j-k of the Directive where they are not within of control of the MAH. These are referred usually by the National Competent Authorities (NCAs), without the consultation of the MAH. Based on the procedure, the MAH will have to pay up to 267.400 EUR before it can defend its product. This can in some instances make a product not commercially viable even though it could be successfully defended. This is a disincentive to the MAH and will ultimately impact patients by denying them certain medicinal products.

   This effect would be worsened by the fact that the proposed fee applies irrespective of the size of the market of non-CAPs. This could in practice lead to withdrawals of MAs since the sales volume of many products will not be able to bear the financial pressure of a referral procedure.

   Furthermore, the proposed amount of 80.300 EUR is inappropriate as a minimum fee for cases involving only a minor workload, e.g. when only a few sentences have to be amended in the information material. It is furthermore crucial to define comprehensive and exhaustive reasons which should be decisive for increasing the already considerable fee of 80.300 EUR for a referral to 267,400 EUR. The proposal does not contain such information.

6. **Consultation Item No. 6: Do you agree with the concept of grouping as proposed? If not, please explain and/or suggest alternative.**

EUCOPE sees the same difficulties as described for the PSURs (see Consultation item no.2).

EUCOPE explicitly rejects an approach whereby multiple payments (e.g. per MAH) of the stated fees would be charged for a referral procedure. The total fee in such a referral could be many times over the fee for a new marketing authorization application in the centralized procedure and would thus be out of proportion.

7. **Consultation Item No. 7: Do you agree with the proposed pharmacovigilance service fee? If not, please explain and/or suggest alternative.**

   EUCOPE considers that no pharmacovigilance service fee should be charged. This fee should be covered by Annual fees and taxes already paid to the NCAs. If not, the MAH is effectively paying two sets of Annual fees whilst there is a reduction of work at the NCAs.

   In addition, the final responsibility for signal detection and evaluation remains with the MAH. The EMA's activities could only be regarded as a "service" if it would shift the task or responsibility from the MAH to the EMA. By contrast, literature monitoring by EMA will only be performed for selected substances and in selected journals.

   Thus, not all companies profit from the EMA's activities and the service fee additionally puts certain companies at a disadvantage. Products with a low risk profile (e.g. homeopathics or herbal medicinal products) have a very low number of adverse events and therefore the expected amount of reportable cases to the Eudravigilance database is negligible. Therefore, at the most a significantly reduced service fee would be acceptable. This is also due to the fact that such companies would not profit from the signal detection service of the EMA. Additionally, for products with a great variety of different substances in different combinations the proposed reduction of service fees for combination products of the same substances is not helpful. This could only be addressed by a cap defining a maximum amount of products considered for the calculation of the service fee.

   Making available the IT infrastructure should be considered as a basic service and be free of charge. The pharmaceutical industry has already put considerable effort in the establishment of the list of products according to Art. 57(2) of the Regulation and is obliged to continuously maintain the content up to date.

8. **Consultation Item No. 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 suggestions how this could be improved.**

   EUCOPE considers it as vital that a 50% fee reduction for PSURs, PASSes assessments and pharmacovigilance referral assessments is granted to SMEs. As stated above, SMEs often have limited resources and need the fee incentives in order to maintain their innovation capacity.

However, even when reducing the fees by 50%, the above mentioned reservations against the proposed amounts of the fees remain. Especially mid-sized companies – not limited to companies which fall under the EU SME definition 2003/361/EC – might struggle to allocate their resources for these obligations. This underlines the importance of a transparent calculation of fees which reflect the actual workload for EMA.

9. **Consultation Item No. 9: Do you agree with the proposed approach with regard to the pharmacovigilance service fee for SMEs (point 3.5.2)?**

   EUCOPE sees the same difficulties described under Consultation Item No. 7 irrespective whether a company is an SME or not.

10. **Consultation Item No. 10: What other aspects would you like to raise? Do you have additional comments?**

    When setting the fees their impact on the overall costs for medicinal products has to be taken into account. Too high fees could thereby jeopardize the pharmaceutical supply and sooner or later lead to a drug shortage, as many pharmaceutical companies will have to reduce their products variety or might not be able to survive at all.

    Another aspect to be raised is related to the specific status of orphan medicinal products: it is understood that the EMA will invoice costs based on the amount of cumulative data at the time of submission and corresponding workload. Orphan indication translates into a very limited patient exposure, subsequently low number of adverse effects included in PSURs.

EUCOPE would appreciate the opportunity to further comment in case the Commission includes additional clarification on the points mentioned above in the Concept Paper.

It is crucial that the general rule set out by the Council Regulation (EC) No 297/95 on fees payable to the European Agency for the Evaluation of Medicinal Products is ensured whereby “the calculation of the amount of the fees charged by the Agency must be based on the principle of the service actually provided”.

European Confederation of Pharmaceutical Entrepreneurs (EUCOPE)

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