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Comments

Comments concerning

Concept Paper

INTRODUCTION OF FEES TO BE CHARGED BY THE EMA FOR PHARMACOVIGILANCE

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Comments

A. General Comments

The BPI wishes to thank the Commission for having the opportunity to comment on the above concept paper.

The general principles in proposing fees for pharmacovigilance – as outlined by the Commission in Chapter 2.3 of the concept paper – are appreciated but the BPI takes the view that especially regarding proportionality and the equal treatment of MAHs the aims are not fully reached and improvements are called for.

Apart from the above, in many aspects the concept paper is not clear enough in its language to understand in what way the stated fees are charged and between which MAHs the stated fees could be divided in which case scenarios. In respect of PSURs, relevant explanations have been given earlier in a Q&A paper by the Commission. But also further questions remain open, which – depending on the Commission's intention – could lead to different comments by the BPI.

Looking e.g. at the maximum fee of 80,300 € for PSUR assessment the question whether this fee is proportionate 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 € 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.

Beside this, it is not discernible on what basis generally and calculation basis in particular the EMA or the Commission, respectively, arrive at the fee frame – assuming that not only centrally authorised but also MRP, DCP and purely national marketing authorisations will be impacted.

Fees need to be calculated adequately and comprehensibly. Against this backdrop, it would make sense for EMA to carry out a pilot project where – using examples of case scenarios – own EMA assessment procedures are played through, possibly in parallel to the already existing (worksharing) processes at Member State level. This could provide a more understandable basis for fees which reflects the real workload and effort involved.

Regarding the fee frame as a whole, it is deplorable that no sufficient consideration particularly of the special features of purely national marketing authorisations can be seen in the Commission proposal. If the fees under discussion are not reduced significantly in particular in cases of purely national marketing authorisations, it is predictable that the distribution of many medicinal products in Germany and other EU Member States is no longer feasible in business economic terms for the impacted companies. This would affect most strongly existing original products with known active substances: the PSUR exemption in Article 107b (3) of Directive 2001/83/EC as amended for generics and well-established use unfortunately does not apply to them so that they fall frequently under the PSUR requirement. Authorised homeopathic or herbal medicines, for which PSURs need to be

submitted, are impacted for the same reasons too. This is also true for ophthalmic medicinal products where due to the specificity of the products and although the medicinal product contains a generic or well-established active substance hybrid marketing authorisation applications are asked for by the relevant competent authorities leading to the situation that the PSUR exemptions of Article 107b (3) of Directive 2001/83/EC as amended do not apply.

Also a number of products have very specific combinations of active ingredients. In these cases the principle of lowering the costs of up to 80,300 € per PSUR by dividing them amongst the concerned marketing authorisation holders does not seem feasible.

If the proposals from the current draft are realised, the BPI sees the danger of many companies having to give up their marketing authorisations, because the high costs for maintaining them will be make them economically unviable. In consequence, the existing problem of drug shortages could become even more severe across the EU, because the – then former – MAHs are no longer drug manufacturers, either.

The BPI asks the Commission to ensure that the fees for holders of purely national marketing authorisations do not increase significantly with the shift of PSUR assessment from national to EU level.

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.

B. Specific Comments

In the following part of this position, the BPI will answer the consultation items the Commission raised in the concept paper.

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

Answering this question depends on the concrete division of this fee, which is very high as such, between the various MAHs. Unfortunately, the current concept paper lacks the clarity necessary in this regard, so that a reply needs to be given based on various interpretation scenarios.

In the concept paper a maximum fee of 80,300 € is stated for each assessment of a PSUR.

We are firmly of the opinion that for products with active substances, which are on the market for many years (10 years at least) and where the safety profile is known as non-critical, much lower fees should be charged than 80,300 €. By using the possibility to group medicinal products, the maximum fee rate for this kind of products should not exceed the total sum of fees charged at present for all EU Member States combined.

Currently, PSURs for products authorised via MRP and DCP and in many cases for purely national marketing authorisations are assessed by the corresponding reference authority (P-RMS). Exemplary costs for PSUR assessment are given hereafter; they are definitely lower as compared to the existing proposal:

	national	CMS	RMS	New Proposal EMA/Commission
	EUR	EUR	EUR	EUR
Austria	500	500	3,600	-
Belgium	1,177.04	1,147.04	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)**

Comments

In some member states, no additional fees are charged for PSUR assessment. PSUR-assessment is included in the annual fee.

Furthermore, overall costs for PSURs resulting from the new legislation can hardly be evaluated by companies. The URD list with substances for which a PSUR will be required has not been finalised. Therefore, it is impossible for companies to calculate costs if it is not known for which substances PSURs have to be written.

It is important to avoid discriminatory treatment of companies that have marketing authorisations in only two or a comparably small number of Member States. For them a PSUR fee of EUR 80,300 is not justified. This is also true for products that qualify for orphan designation but do not have this designation, because the orphan designation was not in place at the point of time when the marketing authorisation application was submitted.

Proposal: The above-stated PSUR fees of the national competent authorities should not be exceeded.

Currently, the fee for PSUR assessment for centrally authorised products is covered by the annual fee (95,000 € for full applications, 23,900 € for generic applications). This approach should not change, because otherwise for the first 8 years only the originator will have to pay the PSUR fee – as generic products cannot be authorised during the data protection period. Moreover, there is no change in workload for CAPS regarding PSUR assessment.

Under EC law, Article 107e of the amended Directive 2001/83/EC prescribes that PSUR assessments shall be performed – depending on the question of whether a centralised marketing authorisation is impacted at active substance level – either at coordination group level (CMDh) or at the Pharmacovigilance Risk Assessment Committee (PRAC). The BPI assumes that the fee – as discussed here – 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 Article 107e (3) of the Directive 2001/83/EC as amended.

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

The possibility of grouping is welcomed in principle.

However, also in this respect the concept paper is lacking the necessary clarity.

In the QUESTIONS AND ANSWERS (Q&A) RELATING TO THE CONCEPT PAPER ON INTRODUCTION OF FEES TO BE CHARGED BY THE EMA FOR PHARMACOVIGILANCE concerning the second question the following is stated: *"If several Marketing Authorisation Holders have submitted one PSUR (because their products contain the same active substance or the same combination of active substances), each one of them would be charged an equal share of the entire applicable fee, …"*

Comments

How is this sentence to be understood? Is the meaning that if several Marketing Authorisation Holders have TOGETHER submitted one SINGLE PSUR (because their products contain the same active substance or the same combination of active substances) each one of them would be charged an equal share of the entire applicable fee? Or is meant that if several Marketing Authorisation Holders have EACH submitted A PSUR INDEPENDENTLY FROM EACH OTHER (because their products contain the same active substance or the same combination of active substances) each one of them would be charged an equal share of the entire applicable fee?

The second interpretation would mean that the fee is seen in relation of the whole assessment procedure in its entirety for all PSURs submitted at the relevant reference date. The EMA would, therefore, look how many different PSURs relating to one active substance were submitted. The assessment procedure starts taking into regard all those PSURs, and the fee of 80,300 € is equally divided between all PSUR submitters.

Should the intention of the Commission be charging a fee of 80,300 € for each single PSUR that was submitted at the relevant reference date the total amount of fees taken in by the Agency for one active substance related assessment procedure would be much higher. In the fictional case that at the reference date 5 different PSURs for a given active substance were submitted by different MAH in the 27 EU Member States this would cause more than 400,000 € of fee revenues for the Agency. Compared to the initial assessment fee for a new CAP (where the assessment procedure includes not only safety related questions but also quality and preclinical issues) this would be totally disproportionate.

Apart from that it would be helpful if the Commission could clarify in which cases different MAH can join to file a single PSUR and hence reduce the costs. Is this possible even in cases where there are different marketing authorisations containing the same active substance and the medicinal products in question are stemming from different manufacturing sites and hence are “physically” not the same? 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?

Apart from the above, a second question remains unclear. In the consultation paper in section 3.1 is stated: *“This maximum amount is equal to the current fee for a Type II variation, based on the scope of the procedure, the extent of the data to be assessed and the workload involved both for PRAC rapporteurs and EMA.”*

What does this mean? Is it planned to have some kind of sliding fee schedule meaning that the maximum fee can be reduced e.g. in cases where the assessment involves only a small workload? Or is the fee a fixed fee, independently from the effort and workload the assessment involves at the level of the Agency or the CMDh?

Should that not be the cases it has to be said that the current proposed fee is seen in relation to CAPs. CAPs normally contain new active substances and therefore the workload for the Agency is until now all about the PSUR assessment of more or less new active substances. Concerning active substances that are on the market for decades the safety profile is well-

known and the PSUR is generally much smaller than this is typically the case for a new substance typically contained in a CAP. This does even mean that the workload for assessing a PSUR for a product with an active substance that is on the market for decades is significantly lower. A fee that is calculated taking into regard type II variations for a CAP does per se lead to an inequal treatment of MAHs having products in the market that are - related to the safety profile - not comparable with a typical CAP for which the fee was originally calculated.

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

The Commission derives the fee frame essentially from the fees charged by the Agency in a centralised marketing authorisation procedure. For example, the fee of 80,300 € corresponds to the EMA fee for a type II variation.

It is not discernible on what basis generally and calculation basis in particular the EMA or the Commission, respectively, arrive at the fee frame – assuming that not only centrally authorised products but also MRP, DCP and purely national marketing authorisations will be impacted. Fees need to be calculated in an adequate and comprehensible manner.

Against this backdrop, it would make sense for EMA to carry out a pilot project where – using examples of case scenarios – own EMA assessment procedures are played through, in order to obtain a more comprehensible, workload and cost-related basis for fees with the help of such a pilot project.

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

This proposal is welcomed in general. The EMA should be responsible for sharing the costs adequately between all MAHs and issue the invoices accordingly. Information on all MAHs is available in the database EVMPD.

As regards the possibility of grouping, it is not fully understandable in which case scenarios this possibility is given.

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

Regarding the fees for pharmacovigilance referrals, a minimum level of 80,300 € is planned. This amount seems disproportionate for procedures involving a very low workload, where e.g. only one single sentence or a few sentences are changed in the information texts.

In case a referral is initiated by the company, costs may be charged to the company. However, these fees cannot be higher as compared to the fee for a centralised marketing authorisation which is 103,800 € for a generic. Current fees for referrals are 66,700 €.

Comments

The newly proposed fees are ranging from 80,000 € to 267,400 €. There is no justification for this increase.

The upper end of the fee frame at 267,400 € seems much too high. The fee stated here is charged for an initial centralised marketing authorisation application where, beside the pivotal clinical trials, also data relating to quality and preclinical data within the dossier of the applicant need to be assessed.

Practically always, referrals are about safety-relevant questions. For this reason, a maximum fee – which refers to the complete assessment of all relevant aspects of a medicinal product (i.e. including preclinical and quality data) – is inappropriate here.

In any case, it needs to be defined finally and conclusively which reasons should be decisive for increasing the already considerable fee of 80,300 € for a referral to 267,400 €. No such reasons are given in the existing proposal and, consequently, cannot be commented upon.

Should the above approach be pursued further, the BPI requests the Commission to state the reasons and to provide an opportunity for comments within a consultation.

Consultation item n°6: Do you agree with the concep t of grouping as proposed? If not, please explain and/or suggest alternative.

This proposal is welcomed in general. The EMA should be responsible for sharing the costs adequately between all MAHs and issue the invoices accordingly. Information on all MAHs is available in the database EVMPD.

As regards the possibility of grouping, it is not fully understandable in which case scenarios this possibility is given.

Concerning referral procedures, the BPI assumes that the stated fee applies for the carrying out of the referral procedure in its entirety and as one single payment, i.e. the fee is distributed between all marketing authorisations involved in the referral procedure and the respective MAHs.

However, should the Commission intend multiple payments (e.g. per MAH) of the stated fees to be made for a referral procedure, the BPI would flatly reject such an approach, because then the total fee in such a referral could be many times over the fee for a new marketing authorisation application in the centralised procedure. This would be totally out of proportion.

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

The annual service fee is not proportionate.

For CAPs this fee is already covered by the annual fee. For nationally authorised products, there is already a grouping fee proposed. Moreover, the workload depends on the nature of the products (extent of use, safety profile). Therefore, the nature of products should be

addressed and a waiver should be granted for products that are authorised in only few Member States or products that are used in small patient populations, exempting them from the fee.

The current concept paper favours companies with MAs of one medicinal product with several strengths in several Member States. Companies who act on national or regional levels and provide a broad product portfolio with different active substances but only a small number of marketing authorisations per active substance are burdened above average. Examples of such companies are distribution businesses or compounders for oncological products selling their medicines to very small numbers of pharmacies or doctors.

Also, it is not clear when and how the EMA can cover the general activities including literature monitoring and monitoring the effectiveness of public health measures. As long as these general activities are not performed there should be no fee. Furthermore, it must be expected that not all medicines will benefit from this service; this applies in particular for substances used in the manufacture of homeopathic products.

In consequence, also in future MAHs themselves will have to carry out literature monitoring. It is also worth noting that companies with products of a good risk profile and small numbers of adverse drug reactions will draw hardly any benefit from the EMA “Signal detection service”. Especially for established original products, authorised homeopathic medicines and also for authorised herbal medicines, this service fee as an annual fee is not proportionate.

Manufacturers of medicines for these types of therapy have a focus in Germany as pharmaceutical industry location.

A common aspect of all of these medicines is that they usually generate rather low sales; regarding homeopathic medicines, only a few hundred packs are manufactured annually for many authorisations. Moreover, authorised homeopathic medicines usually consist of mixtures of various active substances so that for each of these mixtures – as combinations – a service fee would need to be paid individually. Partly, their manufacturers would be impacted with several hundreds of medicines – with the annual fee to be paid for each of them. Obviously, this would cause a very high financial burden.

For the above reasons, no service fee should be charged. Besides, the making available of an IT infrastructure is seen as a general service and should be publicly funded.

Consultation item n°8: Do you agree with the propos ed approach for fee reductions for SMEs as regards the pharmacovigilance procedures at EU level (point 3.5.1)? If not, please explain why and provide suggestions how this could be improved.

Consultation item n°9: Do you agree with the propos ed approach with regard to the pharmacovigilance service fee for SMEs (point 3.5.2)?

Regarding the announced fee reductions for small and medium-sized enterprises, the EU SME definition is to apply.

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Fee reductions for SMEs are welcomed, but linking this with the EU SME definition is not sufficient.

Numerous enterprises, which are mid-sized businesses with low sales from the local perspective, do not fall under this definition; this is in particular because of the limits for the no. of employees. Consequently, the SME approach would not qualify them for fee reduction.

Nationally operating companies with mostly purely national marketing authorisations paying the same fees like Europe-wide or even globally operating businesses would be out of proportion. This makes quite clear that linking fee reductions exclusively with the EU SME definition is too narrow.

This is even true for future marketing authorisations for advanced therapy medicinal products. Although these products will have a centralised marketing authorisation in the future most companies especially regarding tissue engineered products will act at a regional or national level. In an autologous setting the medicinal products will be prepared for an individual patient using his/her own cells or tissue. Hence every single preparation is individual making these products to some special kind of a formula magistralis within the framework of a centralised marketing authorisation. It is quite obvious that in such a setting the sales volumes will significantly differ from typical centralised marketing authorisation. Some companies producing these products are SME others are small but do not fulfil the SME criteria. It is quite obvious that the normal fees discussed here are not proportionate and even financeable, neither for SMEs nor and especially not for non-SMEs.

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

An excessive rate of fees and, therefore, an increase of the overall costs for medicinal products will 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.

It is elementary that older but important medicinal products with low EBITs remain on the market. Quite obviously, this presupposes that their costs are affordable.

Berlin, 15th September 2012 MW