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To: Directorate General for Health and Consumers
Unit SANCO/D/5 sanco-fees-pharmacovigilance@ec.europa.eu

Subject: PC/12/05 – Public consultation on pharmacovigilance fees.

Dear sir, madam,

I am are responding to the public consultation on Introduction of Fees to be Charged by EMA for Pharmacovigilance. This response represents the view and opinion from the perspective of Drug Safety at a generic company in the Netherlands. The work environment and the Member State of residence is thought to be of influence on the opinion on the consultation items. It should be noted that any views, opinions or ideas expressed in this response are those of the author and do not necessarily reflect those of the company (or mother company) where the author works.

In general it is endorsed that fees to be charged by EMA for pharmacovigilance need to be introduced. However, there are some concerns regarding the structure and magnitude of the fees as proposed. In this document response to consultation items 1, 2, 7, 8 and 9 is given. Thereafter some general concerns regarding the proposal are listed in response to consultation item 10.

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

The proposed maximum fee of 80.300 € to be charged per PSUR submitted is disproportional for the amount of tasks to be carried out by EMA.

This can be illustrated by the following 3 examples:

1. In the case of nitrofurantoin there are 16 Marketing Authorisations in The Netherlands. Based on the type of Marketing Authorization procedures one could expect that 4 of the MAHs will submit PSURs (others will probably group and/or will have safety data exchange agreements in place). Assuming the situation is identical in all 27 Member States (Which I am sure it is not, however other than based on assumptions a calculation cannot be made), this means EMA will charge 80300x4x27 = 8.672.400 €. For this amount of money 36 assessors could take 1 year to assess the PSUR assuming they would earn 80.000 € per year and that salary before taxes and employers' expenses equals a single persons salary after taxes x 3.

2. The concept paper states that the fee is proposed based on the benchmarking approach. In principle benchmarking is a good approach, it is however questioned if the fees mentioned in the *Explanatory Note on Fees Payable to the European Medicines Agency (Document EMA/11062/2012, dated 2012-March-28)* are suitable benchmarks to be used for PSUR assessments.
The fact that this document mentions an annual fee for maintenance of a marketing authorisation varying from 66.700 to 95.900 €, while the Dutch Health Authority CBGMEB currently charges only 1000 € annually (which includes PSUR assessments!), makes it doubtful if fees as mentioned in document *EMA/11062/2012* are reasonable and should be used for benchmarking. This is further supported by the fee for renewals which is 13.300 € according to document *EMA/11062/2012.* A renewal normally includes a PSUR (or Addendum to the Clinical Overview (AdCO)). How can a PSUR assessment cost 80.300 € if a renewal including a PSUR/AdCO can be done for 13.300 €?

3. For several substances, PSUR submission by generic companies remains an obligation under the EURD-list. For some of these PSURs there is no possibility to group with other MAH falling under the PV system of the mother company due to the fact that the MAH is the only one in the group having any MAs of the substance. As there is only one MA in one country and it concerns generic products with generally well-established safety profiles (e.g. gentamicin, lidocaine, nabumatone, nitrofurantoin), only a limited amount of safety information will be collected during a PSUR period or cumulatively. Such typical generic PSURs used to be written in about 1 day. Although the new PSUR format requires cumulative information and therefore may take longer to be drawn up, it is anticipated that it will generally not take longer than 1 week. It remains unexplained how a report that could be written within 1 week, costs 80.300 € to be assessed.

If the benchmark approach is to be used, then it needs to be based on figures relevant specifically for PSUR assessments. Such figures are available form a document drawn up by the Fraunhofer institute called *Assessment of the European Community System on Pharmacovigilance* (The same report that fed the public consultation on the Community System and the subsequent development of the new pharmacovigilance legislation). Page 138 of the report states that the median duration of PSUR assessment by European Member States was 30 days (ranging from 1 to 40 days). This mean number of 30 days is a gross amount as the question in the survey asked for the amount of days between receipt of the PSUR and the finished assessment. The number of 30 days for assessment seems to be a good benchmark. Again calculating with a salary of 80.000 € after taxes, which is 240.000 € before taxes and employers expenses, which should be divided into 12 (30 days assessment, not a complete year) this would result in an estimate of 20.000 € needed for assessment of a PSUR. However this is still a too large amount (30 days for assessment was a gross number). It is unknown how much of the 30 days were actually spent assessing the PSUR. Assuming an assessor does not work in weekends and spends some days a month on other tasks an estimate of 12.000 € is needed for an assessment. It should be noted that such a benchmark would be more suitable, but it does still not respect the principle of proportionality and equal treatment of MAHs. The PSUR of the innovator would take much more time to be assessed than the PSUR of a small generic company with only little sales of the relevant product.

There is concern that the anticipated effects of the fee as proposed it that small generic companies that traditionally have a very large product portfolio and only very little margin, are forced to either increase the prices of products for which a PSUR is required or to withdraw such products from the market. Either way Health Care costs would increase, patients would have less freedom of choice of medicinal products and the principle of market economy would be compromised.

I do not agree with the proposed fee for single assessment of PSURs.

An alternative approach to charging fees that respects the principles of proportionality, transparency and equal treatment of MAHs is the following one: It is tracked how many hours EMA actually spends for the whole PSUR assessment procedure (so including all PSURs of all MAHs which are submitted for one single PSUR assessment procedure). The number of hours is multiplied by a standard hourly rate that is reasonable for a pharmacovigilance assessor acting as rapporteur. Subsequently all participating MAHs/ applicants of PSURs, are charged per the amount of product they sold. The amount of product sold is an item to be included in PSURs anyway, so that's no extra work. And I also assume that the total European sales are calculated for each PSUR period anyway, in order to put the numbers of reported Adverse Drug Reactions into perspective. The amount of products sold, is representative for the amount of Adverse Drug Reactions that a companies' product caused, which is in turn representative for the time needed to assess the safety data originating from that company. Although this would increase administrative complexity of the fee structure, it would increase proportionality, transparency and equal treatment of MAHs tremendously.

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

MAHs that belong to the same mother company will already group. Their internal processes set up by headquarters under the responsibility of their European Qualified Person for Pharmacovigilance require them to. These MAHs already share the same Global Safety Database, SOPs, PSUR writing

processes, PSUR planning system, etc under the responsibility of the same EU QPPV. This kind of grouping is not a choice, but a need, a requirement and **I do consider the concept of grouping relevant as proposed, in the situations where local affiliates/MAH share the same pharmacovigilance system.**

If a MAH cannot group with headquarter, because they are the only MAH in the group having the relevant substance in their portfolio or because they are a company not affiliated to or (partly) owned by another company, several obstacles (enforced by the current pharmacovigilance legislation) will hamper grouping with MAHs not belonging to the same company.
In order to create 1 PSUR, a Pharmacovigilance/ Safety Data Exchange Agreement needs to be drawn up. This is a complicated task, that is time consuming and causes extreme administrative burden. Subsequently, such agreements can trigger updates of the Pharmacovigilance Site Master File and depending on the details stated in the Safety Date Exchange Agreement, even updates of Eudravigilance Data (Location of the Pharmacovigilance Site Master File) en variations to the dossier, which in turn triggers fees having to be paid for variations. In addition, if a MAH transfers pharmacovigilance tasks, this could trigger (mutual) auditing, compliance checks, reconciliation, etc, etc. These are all reasons why in many situations MAH have chosen in the past not to group at all especially when the business partner is a pharmaceutical company as well. Each partner using it's own pharmacovigilance system is usually beneficial over grouping (however not always, it depends on commercial agreements between companies and structures of companies as well).
Whereas the new pharmacovigilance legislation was supposed to decrease administrative burden and to free resources to actually detect, assess and prevent harm caused by medicinal products and although the proposed fee structure with grouping supports this and offers the choice of grouping and makes grouping seem beneficial, the current pharmacovigilance legislation hampers grouping with business partners not sharing the same pharmacovigilance system and does not make it beneficial. Effects seem to be opposite in the situation where a MAH cannot group with Headquarter.
Although grouping as proposed may come across as a beneficial choice offered, it really is not.
I do consider the concept of grouping relevant as proposed, in situations where a MAH needs to group with a business partner outside the scope of their headquarters' pharmacovigilance system. However there is concern that other forces will hamper grouping and that it does not have the intended effect.

If the alternative approach to charging fees as explained under consultation item 1 above is followed, each MAH will contribute to the fee proportionate to the extent of harm caused by their product(s) and thus the time needed for the assessor to evaluated the safety date originating from that MAHs; product(s). If a small company has little sales and does not whish to group, it pays a small fee.
If this same small company groups with the mother company/ head quarters or a business partner, it still pays the same small fee (as part of the larger fee charged to the group which submitted the joint PSUR).

Consultation item No.7: Do you agree with the proposed pharmacovigilance service fee? If not, explain and/or suggest alternative.
The statement in the consultation paper that "there is no suitable benchmark for this type of fee" is acknowledged. Indeed there is no suitable benchmark and deciding upon the fee to be charged may be difficult. However a cross check of the proposed service fee against the Annual Report 2011 of EMA shows that the proposed fee is disproportionate.
According to the Annual Report 2011 of EMA, both total revenues and total expenditure are in balance and are approximately 200,000,000 €. It should be realized that these totals include both human and veterinary science, expenditure on buildings, chemical pharmaceutical assessments, etc. The current expenditure on pharmacovigilance is only part of this total expenditure of 200,000,000 €.
In the Netherlands there are currently about 14,000 Marketing Authorizations. About 3,000 of these are CAPs, so there are about 11,000 national MAs for which a pharmacovigilance service fee would become applicable. Assuming that these 11,000 products represent about 2,750 different substances or combinations, MAHs in the Netherlands would need to pay 2,750,000 € pharmacovigilance service fees. Assuming this Dutch situation is representative for the situation in other Member States (Which I am sure it is not, however other than based on assumptions a calculation cannot be made), EMA would receive 27 x 2,750,000 = 74,250,000 € of pharmacovigilance service fee. Is it really anticipated that the total expenditure of EMA will increase by approximately 1/3 as a result of the new

pharmacovigilance legislation only (and note that this is without including the PSUR assessment fee, etc)?

The proposal for the pharmacovigilance service fee needs to be reconsidered taking into account the expected actual increase of expenditure and the numbers of substances and combinations authorized in the European Area.

I do not agree with the proposed pharmacovigilance service fee.

The service fee as proposed does not do justice to one of the key benefits of the new legislation as stated in document *Better vigilance for public health protection – Overview of the new European Union pharmacovigilance legislation* (a flyer published by EMA in 2012), namely "to promote an protect public health and save potentially thousands of lives by amongst others reducing administrative costs (reduced costs and administrative burden)".

Consultation item No.8: Do you agree with the proposed 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.

The public consultation paper mentions possibilities for reduced fees to be paid by Small and Medium Enterprises (SMEs). The Q&A document posted on the website of EMA along with the concept paper suggests a MAH should either group, or try to be registered as a SME in order to benefit in any way ('It is currently envisaged that only SMEs, whose product(s) would be involved in a pharmacovigilance procedure at EU level and which do not wish to group, would need to demonstrate that they qualify as an SME, in order to pay a reduced fee').
Many pharmaceutical companies have a (European) Headquarter and local affiliates in a number of countries. Such a local affiliate will want to group for certain European procedures (and will therefore as part of the large international concern not be able to claim the status of SME). For other procedures such a local affiliate may not be able to group with Headquarter (as Headquarter may not have the substance/product in their portfolio) and may therefore want to claim the status of SME for that particular procedure.
From the consultation paper it is not clear if companies can choose to claim to be an SME per separate European procedure or if they loose the privilege of being regarded as a SME, once they have grouped for another European procedure at any time in the past. In the latter situation **almost no local affiliate/ MAH will be able to benefit from the possibility of reduced fees for SMEs and therefore offering the possibility of reduced fees for SMEs may not have the effect it intends.**
Similar doubts exist for small companies that may want to register as a SME and benefit from the related reduction of fees for some European procedures, but may want to group with other companies for certain other European procedures (e.g. by means of safety date exchange and related Pharmacovigilance Agreements). Thoughtless introduction of fee reduction for SMEs, may have the effect that in order to benefit from that reduction, companies are forced to cancel current safety data exchange procedures (that would support grouping) and related Pharmacovigilance Agreements.

If the alternative approach to charging fees as explained under consultation item 1 above is followed, each MAH will contribute to the fee proportionate to the extent of harm caused by their product(s). Generally SMEs will automatically benefit from reduced fees in that case regardless of grouping.

It is also said that the EMA will facilitate grouping of SMEs by identifying other MAHs with which the SMEs in questions could group. Note that in order to be able to group and comply with legislation Safety Data Exchange'/ Pharmacovigilance Agreements need to be set up This can trigger updates of the Pharmacovigilance Site Master File and depending on the details stated in the Safety Date Exchange Agreement, even updates of Eudravigilance Data (Location of the Pharmacovigilance Site Master File) en variations to the dossier, which in turn triggers fees having to be paid for variations. In addition, if a MAH transfers pharmacovigilance tasks, this could trigger (mutual) auditing, etc, etc. These are all reasons why in many situations MAH have chosen in the past not to group at all and it is questionable if grouping is indeed feasible and beneficial.

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

The statement "As charging of the pharmacovigilance service fee is proposed on the basis of the active substance or combination of substances, SMEs will be charged proportionally less than bigger companies, holding a larger product portfolio" is not true.
An innovative pharmaceutical company having over 1000 or 2000 employees, may have little substances and combinations in it's portfolio while having a large margin/profit, while at the same time a generic company may have only a small amount of employees, very little margin/ profit and easily over 150 substances / combinations in it's portfolio. The number of substances or combinations of a company is not necessarily related to the size of the company, especially when comparing innovative and generic industry.
I do not agree with the proposed approach with regard to the service fee and I think that small companies should be able to benefit from reduced annual service fees. However I expect almost no MAH will qualify as an SME, because the ceilings of an SME status are influenced by the number of employees and profit form the larger group they belong to (http://ec.europa.eu/enterprise/policies/sme/facts-figures-analysis/sme-definition/index_en.htm). Generally small pharmaceutical companies are (partly) owned by and/or affiliated to a larger group.

Consultation item No.10: What other expects would you like to raise? Do you have additional comments?
The concept paper states that "EMA is responsible for coordinating the scientific resources put at its disposal by the Member States". Scientific resources under the new legislation will shift from national Competent Authorities to EMA as many task are no longer being undertaken by Member States but on European level. The new legislation would therefore justify payment of fees to EMA. However, simultaneously fees to be paid to national Competent Authorities should be reduced. **There is concern that fees to national Competent Authorities will not be reduced when fees to EMA are introduced.**

The concept paper suggests that formation of a new scientific committee, namely the PRAC, is one of the reasons that fees need to be collected. However, at the same time a previous scientific working group (PhVWP) with similar composition ceases to exits. The financial statement to the concept paper refers to and acknowledges this ("It is considered that the amendments to the EMEA pharmacovigilance committee structure (including replacement of the existing Working Party) would not lead to an increase in costs compared to the existing costs.").
It is acknowledged that this financial statement is outdated and may no longer completely be valid in view of additional tasks for EMA. However, **a shift from no expected rise in costs to a rise in costs of the magnitude as mentioned in the consultation paper, comes across as absurd and remains unexplained.**

The concept paper states that "The final proposal for introduction of fees for pharmacovigilance will be accompanied by its own financial statement." This is too late. An updated financial statement to go with this concept paper was needed in order to comment on the public consultation. **A public consultation doesn't seem meaningful if respondents to the consultation are not given the input required to adequately form an informed opinion and respond.**

Thank you very much for giving me the opportunity to respond to the proposal.
It is much appreciated.

Yours sincerely,

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