Sanofi Response to the European Commission Concept Paper on the introduction of fees to be charged by EMA for Pharmacovigilance (Ref. Ares(2012)723154)- September 14th 2012

Sanofi recognises that the implementation of the pharmacovigilance legislation widen the tasks of the European Medicines Agency (EMA). As such we agree with the principle of introducing fees to be charged by the EMA to compensate the regulatory authority for pharmacovigilance activities conducted in the context of scientific assessment on medicinal products.

What is of serious concern for Sanofi is the excessive level of the proposed fees, far higher than the ones foreseen in the legislative financial statements issued in 2008 with the Commission legislative proposals. The impact on industry will be unsustainable, in particular for companies with an extensive portfolio of medicinal products registered in the European Union (EU). The deleterious consequence on public health should be carefully evaluated with the companies having to withdraw their products from the market considering that the cost for the life-cycle management activities may exceed the income of the medicinal product..

We consider that the pharmacovigilance activities which are not directly related to medicinal products should receive some Community funding, on the grounds that these activities serve public health and cannot be considered a unique service to industry.

In addition we believe that the revision of the fees system should be done in a wider context to ensure the development of a sustainable and competitive regulatory framework in the EU. It would be important to evaluate the global cost of the post-marketing activities (in particular with regard to the significant payment of fees for variations across the portfolio that are disproportionate to the importance of the change and the assessment required).

Overall Sanofi does not agree with the proposed fees for Pharmacovigilance. In our detailed responses to the consultation items, we are making proposals in order to best comply with:

- the principle of proportionality between the level of fees and the amount of work related to a given scientific assessment by the competent authority;
- the principle of transparency to know what tasks the fee corresponds to and to avoid a task being charged twice;
- the principle of equal treatment of MAHs.

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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 the assessment of PSURs (lower fee of 40,150€ and maximum fee of 80,300€) are too high. These amounts are obviously not comparable with estimates made by the Commission in its 2008 legislative financial statement (6,100€).

We consider that the proposed fees for assessment of PSURs do not comply with the principle of proportionality, in particular for PSURs of products that have been on the market for many years. For most of these products, PSUR assessment cannot be considered as comparable to the data being assessed in the context of a Type II variation:

- The benefit-risk profile is well established.
- Very limited amount of new data (with small number of individual case safety reports).
- Several sections of the PSUR are not applicable (e.g. 'Summaries of the significant findings from clinical trials in the reporting period' as these products are no longer under clinical development).

Setting up a basic fee of 80,300€ for all PSURs concerning products which have been authorised for 2 years or more is inappropriate.

Moreover it is important to concede that for products that have been on the market for many years, the originator will continue to have the obligation to submit the PSUR and pay the PSUR fee, while the generic products that will have most of the market share will be exempted from the PSUR submission and PSUR payment. Proposing a fee of 80,300€ for products which have been authorised for 2 years or more do not comply with the principle of equal treatment of MAHs when the costs are born by the originator company only, unless there are clear provisions that costs should always be shared by any company holding a Market Authorisation for the INN in the EEA..

As several Member States are already charging national fees for PSURs assessment, we would like to get clarification on how the Commission plans to manage this situation in order to avoid a task being charged twice.

Lower fees for assessment of PSURs, more in line with the fee estimate included in the 2008 legislative statement should be established.

We propose to apply the following proportional principles for the establishment of an appropriate range of fees for assessment of PSURs:

- Fee should be minimal for product not yet marketed in any EU country.
- Fee should be reduced when PSUR is due every 6 months for products recently placed on the market in EU.
- Fee should be reduced when the frequency of PSUR submission is one year.
- Fee should be reduced when frequency of PSUR submission is increased (i.e. period between PSURs reduced) as per request of the competent authority.

For truly complying with the principle of proportionality, it is also important to distinguish well-known substance versus new active substance. To determine the appropriate level of fee for PSUR assessment, the following criteria could be used:

- The knowledge of the safety profile for medicinal product that have been placed on the EU market for many years.

- Existence of on-going clinical trials or not (submission of Development Safety Update Report or not).
- Existence of Risk Minimisation Plan or not.
- Number of cases of adverse reactions.

To determine the appropriate level of fee for assessment of PSUR, we consider that using the current fee for a Type II variation as a benchmark is not appropriate. We believe that a more appropriate benchmark would be the fee that is charged to MAH for assessment of a renewal application.. Indeed the renewal assessment is based on a general re-evaluation of the benefit/risk balance of the product after 5 years from initial MA. This seems more aligned with the PSURs that are pharmacovigilance documents intended to provide an evaluation of the risk-benefit balance of a medicinal product at defined time points during the post-authorisation phase.

In addition with the implementation of the new Pharmacovigilance Legislation, the content of the renewal application has been revised. The addendum to the clinical overview now requested as part of the renewal dossier will contain most of the information required in the PSUR. For the most recent products that will go through the renewal process, consideration should be given that the PSUR assessment will duplicate the 5-year renewal assessment. Evaluation of the same information will be charged twice (fee for the renewal and fee for PSUR). This may conflict with the principle of transparency.

Another point of concern is the Concept paper's proposal that the PSUR fee will apply to all products, irrespectively of the registration procedure that was used for granting the MA. We believe that this creates some inequity between the registration procedures. Indeed for CAPs if an action concerning the MA is recommended, there is no longer the need to submit a variation for implementing the change (no additional variation fee), while for non-CAPS, a separate variation will be still required. This system will lead to an overall cost for the PSUR assessment and the implementation of changes concerning MAs of non-CAPs more costly compared to CAPs. We propose that for all non-CAPs, no separate variation fee should be required for the implementation of changes to the MA of non-CAPSs following the assessment of a PSUR. The subsequent variation should be free of charge.

Overall, we do not agree with the levels proposed for the PSURs fees as they do not reflect the real amount of workload required for the assessment of PSURs. We believe that several levels of fees should be defined according to a well-defined model-based approach using the criteria and principles described above. The level of fee for assessment of PSUR should be closer to the amount proposed in the 2008 legislative financial statement, and in any case should not be above what is currently charged for the assessment of a renewal application.

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

In the context of the proposed grouping, we assume that the criteria laid down in the 1998 Communication on the Community marketing authorisation procedures for medicinal products regarding the definition of same applicant/holder will apply. Therefore the proposed grouping will concern independent companies that hold independent marketing authorisations for medicinal products containing the same active substance.

If the prerequisite of "*providing a single PSUR and any other documentation during the procedure*" is maintained this will considerably undermine the possibility of using the concept of grouping for PSUR. From a practical point of view, it does seem unrealistic to produce a single PSUR that will integrate all the information, data and analysis coming from independent companies. We consider more appropriate to establish the concept of single fee in the context of PSUR work-sharing procedure.

- Each MAH holding a MA for a medicinal product containing a specific active substance will submit its PSUR.
- The PRAC Rapporteur or the Member State appointed by the CMDh will perform a single assessment of these PSURs.

The sharing of the PSUR fee across the independent MAHs should be done according to clear rules on how fee assignment will be split in order to avoid imposing complicated relationships between the MAHs which could place them at risk of competition laws infringement. For the fee assignment in the context of the grouping, a model-based approach combining volume of safety reporting and volume of sales of the product may be an appropriate and fair approach that will respect the principles of proportionality and equal treatment of MAHs. It is preferable that the EMA be in charge of assigning the contribution that each MAH will have to pay.

FESS FOR ASSESSMENT OF POST-AUTHORISATION SAFETY STUDIES

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 fee for the assessment of PASS is very high (80,300€), far higher than the estimate laid down in the 2008 legislative financial statement (6,100€). We do not concur that the assessment of all PASSes is comparable to the data being assessed in the context of a Type II variation. PASSes may adopt different designs depending on their objectives and therefore the amount of work required for the assessment of each final PASS report may vary. We consider that the fee should be adjusted according to the methods used for PASS (as described in Appendix 1 of GVP Module VIII), and according to the amount of data collected. In order to comply with the principle of proportionality, we believe that several levels of fees should be defined according to well-defined model-based approach and should be closer to the amount proposed in the 2008 legislative financial statement.

In addition, for a medicinal product that is subject to several PASSes, a reduced fee should be applied, along with the same principles that exist for the reduced fee for Marketing Authorisation Applications.

As for the PSUR, the proposed PASS fee will apply to all products, irrespectively of the registration procedure that was used for granting the MA. We believe that this creates some inequity between the registration procedures (i.e. for CAPs if an action concerning the MA is recommended, there is no longer the need to submit a variation for implementing the change, while for non-CAPS, a separate variation will still be required). Similarly to above, for all non-CAPs, no separate variation fee should be required for the implementation of changes to the MA of non-CAPSs following the assessment of a PASS report. The subsequent variation should be free of charge.

We understand from the concept paper that a fee will be charged at the time of the assessment of the final study report only for a PASS imposed as an obligation. No fee should be required for PASS

initiated voluntarily by MAHs. Also in case of PASS imposed as an obligation, no separate fee should be charged for the assessment of the interim reports of study results. Clarifications will be welcome.

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

The concept of grouping will mostly concern known active substances that have been authorised in the EU for at least 10 years. Possibility of grouping will be extremely limited for new active substances. We recognise that the concept of grouping may facilitate the collaboration between independent MAHs to conduct joint PASSes, as this is foreseen in the pharmacovigilance legislation. However in order to encourage the conduct of joint PASSes, it is important to establish a simple and workable system for the fee assignment with clear and transparent rules on how fee will be split between the independent MAHs. It is preferable that the EMA be in charge of assigning the contribution that each MAH will have to pay in order to avoid imposing complicated relationships between the MAHs, which could place them at risk of competition laws infringement.

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

The proposed referral fees are excessively high (ranging from 80,300 to 267,400€). Once again, the proposed fees are far higher than the referral fee estimates in the 2008 legislative financial statement (72,800€).

Setting up such high fees for pharmacovigilance referrals will irremediably trigger the withdrawal from the EU market of medicinal products that have been used for many years. The regulatory cost associated to pharmacovigilance activities of those products may become inappropriately high compared to their income.

We do not agree with the levels proposed for the referral fees that overestimate the real amount of workload required for the assessment of a referral, in particular for the maximum referral fee being proposed. In no case a referral assessment can be comparable to a full benefit-risk assessment. Most of the data/information submitted in the context of a referral procedure have already been previously submitted and assessed as part of the standard regulatory activities of the medicinal products involved in the referral procedure. In particular, the non-clinical data provided in an initial dossier are rarely reassessed during a referral procedure.

Up to now referral procedures were free of charge (excepted for the Article 30 or Article 31 referrals initiated by the MAH for which a referral fee of 63,400€ is charged). According to the appointment principles for PRAC Rapporteur and Co-Rapporteur in case of pharmacovigilance referral (as defined in the EMA document (EMA/315258/2012) of 28 June 2012), the co-rapporteurship is automatically granted to the Member State triggering the referral when non-CAPs or mixture of CAPs and non-CAPS are involved. Considering that the scientific assessments by PRAC Rapporteur and Co-Rapporteur should be subject to payment of half the fee (as mentioned in the 2008 legislative financial statement), a special attention should be given for not creating a bias in the system by

setting up very high referral fee that may be unduly seen as a potential important source of revenue that can be disproportionate to the importance of the scientific assessment required.

We understand the need for an industry contribution to ensure the sustainability of the pharmacovigilance system and therefore we may agree with the principle of creating a fee for assessment of pharmacovigilance referrals. However we strongly believe that the level of fee pharmacovigilance referral should be reasonable, remaining within the range of what is already in place for referral initiated by MA. This is the only way to avoid negative consequence on public health with products disappearing from the market and to allow companies to forecast a realistic budget. Also, we suggest that the fee system includes a 'safeguard' clause i.e. if no major action on the MA of the products concerned by the referral procedure is recommended as an outcome of the referral procedure, no fee should be charged.

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

The concept of grouping is already implemented under the current Fees Regulation for certain referrals initiated MAHs. While we welcome the extension of the grouping concept to pharmacovigilance referrals that will involve different MAHs, it is important to establish a model-based system for the fee assignment that complies with the principles of proportionality and equal treatment of MAHs, as well as with competition laws. It is preferable that the EMA be in charge of assigning the contribution that each MAH will have to pay.

PHARMACOVIGILANCE SERVICE FEE

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

We do not agree with the creation of the pharmacovigilance service fee. Annual fees are already in place in most the Member States for non-CAPs. This annual fee aims at covering all aspects of routine dossier management and maintenance, including the work associated with on-going pharmacovigilance activities. We consider that the proposed new pharmacovigilance service fee will duplicate the national fees. This is not compliant to the principle of transparency (same work being charged twice).

The same comment is valid for CAPs, which are already subject to the annual fee covering pharmacovigilance activities. On this particular point, we believe that an overall review of the annual fee for CAPs products is necessary in order to have more transparency on what tasks the annual fee corresponds to.

The concept paper lists a number of activities that should be financed by the proposed pharmacovigilance fee. We consider that they are not directly product-related activities. They relate to telematics projects and public health activities and as such they should be financed by Community funds.

FEE INCENTIVES FOR MICRO, SMALL AND MEDIUM-SIZED ENTERPRISES AS REGARDS PHARMACOVIGILANCE

Consultation item n°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 proposed approach for fee reductions should not be limited to the SME status of the MAH. We believe that special categories of products such as orphan products should also be eligible for such approach. Reducing the cost of life-cycle management activities for orphan MAs is an important incentive that will contribute to stimulate the development of orphan medicinal products. The EMA has already implemented a fee reduction policy for orphan medicinal products in the pre-marketing authorisation phase. This policy should be extended in the post-authorisation phase for allowing pharmacovigilance fee reductions.

The same policy could be extended to products on the market for a long time which have a very narrow indication left and for which there are no alternatives available, as for such products the cost for the life-cycle management activities may exceed the income of the medicinal product.

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

See our response on consultation item n°7.

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

No additional comment.