EuropaBio comments on EC PV fee concept paper

EuropaBio supports the need for the EMA to be appropriately funded to deliver a predictable, timely and quality service to all its stakeholders and the innovative biopharmaceutical industry is willing to pay reasonable fees for the services provided to it. EMA should be financed in a sustainable manner to ensure it can fulfill its extended mission under the new pharmacovigilance legislation to protect European public health while enabling medical innovation. In this respect, we agree with the Commission's general principles in proposing fees for pharmacovigilance (i.e. proportionality, transparency, equal treatment of Marketing Authorisation Holders (MAHs), minimal additional administrative complexity), but believe that the current proposals are not fully in line with these principles.

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

In the current economic climate, and in view of increasing regulatory requirements and global competition for funding investment in research and development of innovative products to meet unmet medical needs, simple, predictable and reasonable regulatory fees are needed, wherever possible. The PV fee proposals must not inadvertently create an incentive to increase the number of requests for safety reviews by the respective authorities. A significant increase in the post-authorisation cost of medicines carries a risk of deterring some developers from registering new medicines in Europe or of leading to de-registrations and the withdrawal of therapies from the market. This may particularly be an issue for SMEs and/or for products with relatively low returns. Instead of fostering, this could undermine DG Sanco's strategy to broaden the availability of new medicines on the EU market.

EuropaBio believes that the proposed fees in the concept paper are disproportionately burdensome for the innovative industry. The proposal fails to provide a transparent justification related to specific allocation of resources to the various regulatory activities and to actually incurred costs, including overheads. They further fail to acknowledge that these pharmacovigilance activities constitute a service to public health, in addition to (or even rather than) a service to marketing authorisation holders.

Although the concept paper states that a review of regulatory fees in general is not part of this consultation, we would strongly encourage using this opportunity for an urgent review of the overall fee Regulation. The aim should be to simplify and streamline registration costs and ensure that there are no unintended incentives for Regulatory action.

Furthermore, EuropaBio believes that the Commission's general principles in proposing fees for pharmacovigilance, as described in section 2.3 of the Concept Paper, are currently not met by the Commission's proposals for the following reasons:

Proportionality

The Impact assessment and Financial statements that accompanied the Commission's original December 2008 proposals for the Pharmacovigilance legislation included estimates of a total budgetary impact for Industry and regulators. These documents noted a total increase of fees

payable to the EMA of € 10.596M[1] for the pharmacovigilance activities that would newly attract fees (see table below.).

Procedure	# per year	Fee per procedure	Annual income
Referral	20	72.800€	1.456 m€
PSUR assessment	1000	6.100 €	6.100 m€
PASS assessment	300	6.100 €	1.830 m€
RMP assessment	100	12,100€	1.210 m€
Total			**10.596 m€**

This estimated additional income based on Industry fees (detailed above) would generate a surplus of around €0.5M pa when the estimated EMA costs for the performance of these additional PV activities was deducted.

We note that the estimated fees for PSUR and PASS assessments in the impact assessment were less than 10% of the fee levels proposed in the concept paper. Based on the proposals in this concept paper, and the same expected workload for referrals, PSUR and PASS assessment as in the 2008 Financial Statement, the minimum estimated additional EMA annual income from fees would be between **€65M** (assuming that all referrals and all PSURs would attract the lowest fees) and **€105M** (if all PSURs attracted the higher fee). It should also be noted that these figures do **not** include the income from the proposed annual service fee.

While we recognise that the final adopted legislation is not identical to the 2008 proposal, and that costs may have increased due inflation since then, it is difficult to believe or accept that the costs to EMA for fulfilling the covered duties have increased so substantially. Applying a generous 5% inflation rate would only take the estimated costs to €12.257M, leaving a surplus of between approximately €50M and €90M (more, when the annual service fee is taken into account). Even if the current Community contribution were fully withdrawn (which we do not support), EMA would still have a surplus. These figures suggest that the level of the fees is not proportionate to the work being carried out.

The lower fees in the 2008 proposals are more closely aligned to the current fee levels to be paid to national Regulatory agencies for these services. However, most EU countries do currently not charge fees for Pharmacovigilance activities or cover those expenses through an annual maintenance fee including supervision and inspection activities (see attachment 1).

In addition, the contribution of other stakeholders and public actors to the co-funding of pharmacovigilance activities that were shifted from the national level to the EU level, in order to rationalize the system as a whole, is unclear.

Although we acknowledge that Recital 24 of Regulation (EU) No 1235/2010 states that 'The Agency should be enabled to fund these activities from fees charged to marketing authorisation holders', it is not implicit that MAHs should be the only stakeholder to fund the enhanced

[1] http://ec.europa.eu/health/files/pharmacos/pharmpack_12_2008/pharmacovigilance-ia-vol1_en.pdf

pharmacovigilance requirements. It would be of interest to know what percentage of the pharmacovigilance costing is to be borne by MAHs and what percentage will be provided by Community funds. The general public will be the principal beneficiary of enhanced pharmacovigilance systems.

Transparency

A simple comparison of one procedure to another procedure without a detailed and transparent cost calculation is not acceptable; specifically as no real work experience based on time recording under the new processes exists at this stage.

A simplified and transparent system is required, allocating resources to the EU or national level on the basis of the occurrence of the service, complemented by adequate resourcing from the public sector to support additional public health services which the agencies provide.

This has already been pointed out in the Ernst & Young Report (2010)[2]: The EMA compensation system should be clarified, and a funding system identified for non-fee paid activities.

Equal treatment of MAHs

While MAHs are treated in an equal manner in relation to fees for actual service, adequate and fair contributions from other stakeholders that also benefit from the strengthened public health system are lacking. In addition to SMEs, orphan medicinal products, and products approved under exceptional circumstances should be considered for fee reductions.

Minimum additional administrative complexity

We generally believe that the current and proposed European Regulatory fee structure fails to provide a simple and predictable system.

For example, a range of fees is proposed for safety-related referrals, but there is no clarity as to how the fee for a specific referral will be determined, nor how this will be applied consistently for different referrals.

No duplication - Although it is clear in Recital 24 of Regulation (EU) No 1235/2010 that: 'These fees should not cover tasks carried out by national competent authorities for which such authorities change fees in accordance with Directive 2001/83/EC', in order to avoid such an eventuality we would welcome full transparency of the activities included in each fee. The proposal should also make clear that individual member states must not charge duplicative fees for pharmacovigilance activities linked to centralised marketing authorizations.

Level playing field - Similarly situated marketing authorisation holders should be treated alike. Apart from the above consideration relating to orphan/low volume/sales products, the issue of whether the product is an originator or a generic/biosimilar does not seems to be relevant factor. We would welcome transparency about the way the fees will be fairly and equally divided among similarly situated MA holders.

Use of the term 'Industry' – It is noted that in Recital 24 of Regulation (EU) No 1235/2010 states that 'The Agency should be enabled to fund these activities from fees charged to marketing

[2] http://ec.europa.eu/health/files/pharmacos/news/emea_final_report_vfrev2.pdf (Page 198)

authorisation holders', however there are four instances where the fee payer is referred to as industry implying a wider audience than simply the marketing authorisation holder. We request that for transparency 'industry' is replaced with 'marketing authorisation holder' so that there can be no ambiguity as to who should pay for these pharmacovigilance activities.

Independence of assessment - Although it is explicit in Recital 24 of Regulation (EU) No 1235/2010 that the Agency can fund pharmacovigilance activities by charging marketing authorisation holders a fee for service, as a general principle we consider that this is a flawed approach.

The notion of introducing a series of compulsory activities which will enhance pharmacovigilance for products marketed in Europe which will therefore be a benefit to society as well as the marketing authorisation holders and then mandate payment by marketing authorisation holders could be perceived by some as leaving the Agency as less than independent where they are reliant on the fees gained for an imposed service.

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

We do not agree with the proposed fee for single assessment fee for single assessment of the PSUR. PSUR assessments under the new law constitute a risk/benefit assessment. This concept already existed for Renewal assessments in the past (Article 24(2) of Directive 2001/83/EC). As such and in the absence of any transparent cost calculation, we believe that the PSUR assessment must rather be compared with the workload for a renewal assessment than a Type II variation.

The current basic fee for an EU renewal procedure is 13300Euro[3] which corresponds much more closely to the estimated fee level in the Commission's impact assessment as well as current PV fees charged by national Regulatory agencies.

It is also worth noting that PSURs under the new legislation will include less data, in the form of line listings and narratives. In addition, while the Concept Paper says that assessment of PSURs is based on cumulative data, the Commission Implementing Regulation (EC No 520/2012) requires that the PSUR shall focus on new information since the data lock point of the last PSUR. These factors could potentially simplify the regulators' assessment of PSURs.

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

We generally support a concept of grouping which reflects the actual workload performed for the assessment and which allows for the sharing of cost across several medicinal products including the same active substance. Only additional administrative costs should be charged in these cases. The amount should be compared to the current national fees and reflect the actual additional work to be performed.

Nevertheless, the proposal for the grouping fees for assessments of PSURs is not completely clear, and our position depends on the definition of "same MAH" and "different MAH" being applied. It should be confirmed that the usual Commission definition of "same MAH" is being applied: i.e. all companies in same group of companies or companies that have concluded agreements are considered the "same MAH", and therefore pay only the "basic" PSUR assessment fee. If this definition is not being applied, such that affiliate or local operating companies in different MS are regarded as different MAH, the grouping concept is not supported.

If a single assessment is conducted for more than one "different" MAHs (e.g. innovator and multiple generics) then the concept of grouping seems reasonable. The concept may, however, introduce complexity with regard to how the participating MAH divide the costs between themselves.

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

[3] http://www.ema.europa.eu/docs/en_GB/document_library/Other/2012/03/WC500124904.pdf

We do not agree with the proposed fee for assessment of PASS. The proposed fee is more than ten times greater than what was proposed in the 2008 Financial Statement, yet there is no clear justification for this increase. A fee comparable with Type II variations does not seem reasonable for the assessment of a single PASS: Type II variations may be more complex and may include results of more than one study; the results of a PASS may not have an impact on the marketing authorisation. It should also be noted that, if the results of the PASS do require the update of the product information, a variation fee will be charged. The MAH should not face two separate fees for these related activities. Incentivizing increasing numbers of PASS imposed by Regulators due to economic motivations should be avoided.

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

Our understanding is that the grouping applies when different MAH conduct **joint** PASS. If this understanding is correct, the concept of grouping seems reasonable.

As above, under Consultation Item no 2, it should be confirmed that, for non-Centralised products, the usual Commission definition of "same MAH" is being applied.

In addition, we suggest that grouped submissions of several PASS study reports for review as well as grouping with other type II variations should be encouraged to ensure the efficient use of regulatory resources post-approval.

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.

No. The proposed fees could be significantly greater than the current fee for a referral initiated by the MAH (€66700), and no clear justification has been provided. A maximum fee of €247600 is proposed for referrals requiring a "full benefit/risk assessment", comparable to a new MAA. This comparison makes no sense: assessment of a new MAA entails the review of not just clinical, but also CMC and nonclinical data. In addition, at the time of a new MAA, the product is largely unknown to assessors, who will have to "start from scratch" in their assessment of the entire dossier. In a referral, the focus is on the new information that was the trigger for the referral (albeit in context of what is already known).

The current proposal does not provide any opportunity for MAHs to consider those fees in their budget planning cycles. Transparency regarding the actual costs incurred by a specific EU Referral procedure is not obvious from the current concept paper, neither the contribution from other involved stakeholders. In contrast, single Member States can unilaterally request EU level safety Referral procedures based on subjective and non harmonized risk/benefit thresholds across the European Regulatory Medicines Network. Even if the outcome of the procedure is negative, the MAH has to invest significant resources during the referral process to discuss the issue in question, but also in relation to the unpredictable cost. This is a major fault in the proposed mechanism.

Such a system may contribute to a situation when some MAH might consider de-registering those medicines that provide a low return, to minimize the risk of financial exposure due to safety referral procedures.

The assessment of referrals should be considered more a public health service, rather than a service to industry particularly when the referral is initiated by regulators. It could be argued, therefore, that at least a proportion of costs should be supported by the Community contribution to the EMA.

If a fee is to be levied on the MAH, it would be preferable to keep the fees for referrals simple, with only one fee to be charged for all referrals started by the MAH[4]. While there will be a spectrum of complexity of referrals, when the costs are considered across several procedures, the net income from fees should cover those costs.

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

Please see our response to consultation item no. 4.

In addition, the Concept Paper states that the average number of MAHs in referrals was 116 in 2009 and 139 in 2010. It is not clear whether this is counting affiliate and local operating companies as separate MAHs. If it is, then it is disingenuous to suggest that grouping will proportionally decrease cost per applicant/MAH, as the total cost to the group of companies should be considered.

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

We agree that MAH's should contribute according to their product portfolio size to the general maintenance of EudraVigilance and the PSUR repository to ensure adequate funding for efficient development of these tools. It should be noted, however, that not all MAH will benefit from the literature monitoring to be performed by EMA, so it does not seem reasonable that all MAHs should bear the cost of this service.

As with consultation items 2, 4 and 6 above, the notion of “same MAH” also needs to be considered here. For non-Centralised products, the fees will increase dramatically (and disproportionately) if each affiliate or local operating company is regarded as a different MAH.

For simplification, this fee should become part of the annual maintenance fee.

We strongly support adequate financing of the European Medicines Agency activities to ensure the overall objectives of Regulation 2010/1235. However, Recitals 13 and 24 of that Regulation do not explicitly state that all activities need to be financed by MAHs fees. We believe that further co-financing by Member State and Community budgets is necessary to realize the expected common European public health benefits.

[4] I.e. such system is currently in operation in Germany

Consultation idem 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.

For SMEs developing innovative medicines, centrally authorised therapies such as ATMPs, the introduction of the newly proposed PV fees in addition to the current annual post-authorisation fees (of which 30% is already foreseen to fund PV-related activities), increases the administrative cost in the first 5 years post-authorisation. A simulation to illustrate the significant budget impact increase of 167% (from 420K to a total of 700K) is provided in attachment 2 (tables 1 and 2). This example highlights that the current proposal could potentially lead to significant and disproportionate increases in the standing costs.

Currently, only micro-sized enterprises would be exempt from the new fees, while other SME's could only benefit from a 50% reduction. A further categorisation might however be necessary to motivate SMEs to register innovative therapies in Europe.

- The first years post-authorisation frequently present the most difficult financial years, especially for small scale companies with a limited product portfolio. Indeed, SMEs with such innovative CAPs will often not be able to immediately cover the entire territory and frequently also face additional challenges with respect to pricing and reïmbursement negotiations for first in class products not (fully) corresponding to the classical Health Technology Assessment rules. As such, sales volumes only gradually increase over time while the investment climate in a commercial entity differs from a pure R&D stage.

- Innovative CAPs like ATMPs are often prone to increased investment for risk management and education in the first years post-authorisation because of their novel character. The current annual fees in addition to this continued investment in the product already presents a significant financial commitment in those first years.

- The current proposal foresees a 50% reduction in the first two years post-authorisation. However, as the first market introduction not always immediately connects to the authorisation and as such PV activities are limited in the interim period, it would be welcomed if this provision could be reworded to a 50% reduction in the first two years post-marketing.

A similar approach is proposed to be adopted for orphan products and for products approved under exceptional circumstances, for all fee categories, irrespective if the MAH is SME or not.
In addition, we propose to define a revenue limit per approved drug below which no fees are charged to ensure continued research and investment in those products.

We welcome that a reduced fee level be introduced for micro-enterprises and for SMEs, but consider that this reduction should go further and also cover orphan-medicinal products and other low volume/low sales products which might otherwise be withdrawn from the market due to the additional costs associated with post-marketing activities.

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

It is appreciated that with the new system, additional fees for PV-related variations are no longer charged. In the current proposal, it seems that this incentive is used to justify the pharmacovigilance service fee. However, in the context of this incentive it is important to consider the entire impact of the new fee system and not just at the service fee. Nonetheless, it is supported that the costs of the system are carried by all involved stakeholders and as such the concept of a low cost pharmacovigilance service fee for SMEs.

Attachment 1

Overview of national pharmacovigilance fees

Austria	PSUR National: 500 € PSUR MRP/DCP RMS: 3600 € PSUR MRP/DCP CMS: 500 €
Belgium	PSUR full cycle: 1.210,90 € PSUR short cycle: 605,45 € PSUR MRP/DCP - RMS products: 2.421,80 €
Bulgaria	No fees
Cyprus	No fees
Czech Republic	No fees, annual maintenance fee 19500 CKR (762 €)
Denmark	PSUR National : DKK 6.494,- PSUR MRP/DCP (RMS): DKK 12.994
Estonia	PSUR MRP/DCP RMS: 320 € per year Annual maintenance fee 160 € Full fee waivers if sales below certain threshold
Finland	
France	No fees
Greece	PSUR review: no fee
Germany	PSUR National: 1.300 € PSUR MRP/DCP RMS: 4.400 € PSUR MRP/DCP CMS: 1.300 €
Hungary	No fees
Iceland	PSUR national: 275.000 ISK PSUR MRP/DCP RMS: 385.000 ISK PSUR MRP/DCP CMS: 16.000 ISK
Ireland	PSUR review: No fee DSUR review: 170 €
Italy	No fees
Latvia	PSUR National: 1000 LVL (1423 €) per INN Annual maintenance fee: 350 LVL (500 €)
Lithuania	PSUR national: 212 € (+61 € per additional strength or form) PSUR MRS/DCP RMS: 971 € (+172 €) PSUR MRP/DCP CMS: 138 € (+40 €)
Luxembourg	No fees, only annual maintenance fee 12.39 € per form and strength
Malta	No fees
Norway	No fees
Portugal	No fees
Poland	No fees
Romania	No fees
Spain	PSUR National: 6 or 12 mo PSURs: 375.17 €

	3 yr PSURs: 2272.48 €
Sweden	No fees
Slovakia	No fees
Slovenia	PSUR National: 1500 € PSUR MRP/DCP - CMS products: 250 € PSUR MRP/DCP - RMS products: 11.750 €
Switzerland	PSUR fee (as of 2013): CHF 1500
UK	PV fees included in annual maintenance fee, e.g. NAS yearly fee 23.025 Pounds

Attachment 2

Impact of newly proposed PV fees on post-MA cost structure (assuming new fees would have been applied retro-actively)

Table 1 Post MA fees prior to new PV fees

Period	Annual fee[1]	Reduction	Total
Year 1	90200	50%[2]	45100
Year 2	91100	NA	91100
Year 3	93000	NA	93000
Year 4	95900	NA	95900
Year 5	95900	NA	95900
Total			**421000**

[1] Regulation 297/95 as amended

[2] Regulation 1394/2007, article 19

Table 2 Additional PV fees (simulation applied retro-actively)

PSURs	PSUR fee[1]	PASS[1]	PV service fee	Total
1 (6m)	20075	0	0	20075
Initial placing on the market				
2 (6m)	20075	0	1000	21075
3 (6m)	20075	0	0	20075
4 (6m)	20075	0	1000	21075
5 (6m)	40150	0	0	40150
6 (1yr)	40150	0	1000	41150
7 (1yr)	40150	40150[1]	1000	81300
8 (1yr)	40150	0	1000	41150
Total	240900	40150	5000	**286050**

[1] 50% SME fee reduction

Attachment 3

As outlined in this example of an allergen manufacturer, the proposed fees are not viable for very specific products. The proposals do not take into account the particularities of allergen manufacturers and their specific field of allergy diagnosis and treatment.

This company has around 400 employees, is specialized on in vivo diagnostics and specific immunotherapy (SIT) of type I allergies and holds 1515 marketing authorizations. These currently result in 12 different grouped Periodic Safety Update Reports (PSURs). When considering the regular PSUR period of three years and adding the PSUR fees plus the Service Fees the total amount this company would have to pay is 5.5 mio € over the three years' period. In comparison, in 2011, the company generated only 60% of turnover with preparations with marketing authorizations in Europe. The expenditures for pre-clinical and clinical development of innovative new drugs for allergic patients, amount to about 20 mio EUR per product and allergen.

When taking into account these particular figures, it becomes obvious that the proposed new fees are at least in the specific field of allergen products not acceptable. This additional and extraordinary burden for allergen manufacturers is not in a reasonable proportion to the alleged long-term benefit for the public health as the main objective of the Regulation.

It should be noted that allergen manufacturers have already recently invested considerably in the development and approval of their many products with increased requirements according to new European regulations, e.g. to conduct extensive additional studies to meet new validation requirements.

For micro, small and medium sized enterprises (SMEs) the draft offers the possibility of a fee reduction by 90%. But regarding the staff headcounts (250 at maximum) the respective Regulation (2003/361/EC) cannot be applied to allergen manufacturers. Higher numbers of employees are necessary because of the high demands in production and quality control in allergy products. Still, the proposed numerous fees would constitute an inadequate financial burden for this company.

In summary, the Commission's proposal threatens the economic survival of allergen extract manufacturers and therefore potentially jeopardizes the care of allergic patients. As a consequence, less financial means would be available for research and the conduction of clinical studies and thereby developing and enhancing existing products.