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European Commission

Health and Consumers Directorate-General

IMPLEMENTING MEASURES IN ORDER TO HARMONISE THE PERFORMANCE OF THE PHARMACOVIGILANCE ACTIVITIES PROVIDED FOR IN DIRECTIVE 2001/83/EC AND REGULATION (EC) NO 726/2004

Public Consultation

CELGENE Europe Ltd. Contribution

Celgene Corporation, headquartered in New Jersey, USA and operating as well in 22 EU Member States, is an integrated global biopharmaceutical company engaged primarily in the discovery, development and commercialization of novel therapies for the treatment of rare cancers and inflammatory diseases.

Highly effective drug safety and risk management is central to our company and our company philosophy. It is from this perspective that Celgene Corporation, hereby represented by Celgene Europe Ltd, its UK European Marketing Authorization Holder, would like to thank the European Commission for this opportunity to comment on the future implementing measures on pharmacovigilance.

In the following contribution, responses are given only to the points where the Company felt it needed to add to the assessment of the consultation paper or should provide an answer.

A. Pharmacovigilance system master file (PV SMF)

1. Definition

Celgene welcomes the possibility of applying separate pharmacovigilance systems for different categories of medicinal products.

3. Content

On the requirement that the PV SMF is located at the site where the QPPV operates, we understand that if a electronic version is available as well as 'a clearly arranged printed copy can be made available for audits and inspections' on that site, this would indeed meet the criteria. If this is not the case we would suggest that this is clarified in the text of the implementing measure.

In relation with paragraph (7) (b), we suggest that a definition of what a "description of the resource management for the performance of PV activities" is included in the section 13 on resource management under "C. Quality systems for the performance of PV by MAHs". A suggestion is made with the comments referring to that section.

On paragraph (7) (c), we suggest that "records of qualification" are limited to the curriculum vitae of the individuals performing pharmacovigilance activities to ensure alignment on the interpretation and simplification.

Consultation item no. 1: Should additional processes and pharmacovigilance tasks be covered?

We don't recommend any additional processes to be covered.

4. Maintenance

Celgene very much welcomes that changes to the PV SMF will be no longer subject to variation obligations, however, on the proposed ideas regarding the maintenance of the PV SMF and notifications to authorities, Celgene would like to offer an alternative proposal on the maintenance of PV SMF which it feels would still meet the objectives of the legislation but would be more practically applicable.

The text under consultation includes that the information in the PV SMF "shall be continuously kept up to date, and where necessary shall be revised to take account of experience gained, technical and scientific progress and amendments in the legislative requirements".

This requirement would go beyond the scope the current legislation and will create more administrative work and costs. A continuous maintenance of the PV SMF would be a too burdensome requirement for MAH without any added value to the supervision tasks or the safety of the products. Considering the possible frequent changes in personnel, contracts, systems - such as the guideline of the International Conference on Harmonisation (ICH) E2B reporting requirements and possible corrective and preventative actions (CAPAs) that might be implemented - the requirement to keep the PV SMF "continuously" up to date would be very demanding and resource-intensive for companies. This might be particularly challenging for companies with few employees and in particular for those with a large number of products, such as generic companies.

An annual or 6-monthly update of the PV SMF incorporating all the different updates would result in a more accurate document and it would be much more practicable for the industry. This would also allow having version controls of the document (vs. a living document). This will also be helpful for inspections of the PV SMF as it allows providing a clear status of where things stand historically.

As maintenance on an ongoing basis would not be feasible, it is a good idea that the PV SMF contains the date of when it was last reviewed.

We would suggest thus the following text for section 4 on Maintenance of the PV SMF:

"The information of the pharmacovigilance system master file should be succinct, accurate and reflect the current system in place. It should be ~~continuously~~ ***regularly*** *kept up to date,* ***reviewed on an annual (or six months) basis****, and where necessary, shall be revised to take account of experience gained, technical and scientific progress and amendments in the legislative requirements.* ***The PV SMF shall include the date of when it was last revised. Information about changes /modifications to the master file shall be made available to the competent authorities on request.***"

Consultation item no. 2: The aim of the pharmacovigilance master file is two-fold: to concentrate information in one global document and to facilitate maintenance by uncoupling it from the marketing authorisation. Therefore changes to the content of the master file will be no longer subject to variation obligations. Would it be nevertheless appropriate to require the marketing authorisation holder to notify significant changes/modifications to the master file to the competent authorities in order to facilitate supervision tasks? If so, how should this be done? Should the master file contain a date when it was last reviewed?

On the question whether **significant changes / modifications** to the PV SMF should be notified to the authorities, this requirement would also create an important administrative burden with no real added value. Authorities' supervision tasks are already ensured by the inspection programme. The PV SMF can be made available at any time to the competent authorities. It is also questionable whether authorities would be able to cope with all this information. Regular submission would undermine one of the reasons for changing from the detailed description of pharmacovigilance system (DDPS) to the PV SMF as the DDPS required notification of the changes to the Agency.

Additional guidance on what "significant changes" might mean would also be needed otherwise this would leave a lot room for interpretation and may result in all changes to be notified.

As proposed above a more practical system would be to make thorough and quality controlled updates to the PV SMF once or twice per year.

5. Documentation

The requirement to note in the PV SMF "any current deviations from the pharmacovigilance procedures, their impact and management until resolved" goes beyond the scope of the current legislation and therefore we feel that it should not be included in the text of the implementing measures. At any rate companies should have a process in place to manage deviations as part of their quality management systems but this should not be part of the PV SMF. This would blur the content of the PV SMF and again result in a lot of unnecessary and burdensome administrative work.

The proposal to have a "logbook recording any alteration of its content within the last five years" seems to be a difficult requirement to implement. Considering the continuous changes this would result in a very long unreadable logbook and also in extreme efforts to handle the logbook without any adding any value to the content of the PV SMF.

Therefore an annual or 6 monthly review of the PV SMF with identified changes mentioned in the logbook would be more practicable and accurate. This would also be the version to be made available for inspections of ad hoc requests.

6. Delegation

Celgene has concerns about the second paragraph of this section:
"In those cases the PV SMF shall contain a description of the delegated activities and/or service provisions relating to the fulfillment of PV obligation, indicating the parties involved, roles undertaken and concerned product(s) and territory(ies). Copies of the signed agreements shall be included in the master file. "

Celgene feels that it is not practical to include copies of all agreements in the PV SMF. The number of agreements is very numerous. "Service provision relating to the fulfillment of pharmacovigilance obligations" could encompass nearly any agreement with an adverse event clause. The file would have to be updated every time an agreement is revised or amended. And these agreements might include business confidential information not relevant to the safety of the product, and therefore should not be part of the PV SMF.

Companies could alternatively provide a list of companies to which they have outsourced the PV activities with a description of the activities performed by the contracted party and copies of the PV agreements could be provided in an inspection context.

Consultation item no. 3: Is it necessary to be more precise on potential delegation, e.g. in the case of co-marketing of products? Please comment.

No, unless the expectation on the information required for the PV SMF for co-marketing of product delegation differs from those requirements already stated.

7. Audit

The consultation text states that: "Immediately after an audit report has been received that requires corrective or preventive action, the MAH shall place a note concerning the main findings of the audit on the PV master file".

Celgene has concerns over the word "immediately". Besides the possible confusion over the interpretation of what "immediately" means (24 hours?), it could prove difficult and unrealistic to expect for companies with many affiliates and/ or outsourced PV tasks to multiple vendors and with a lot of co- marketing products to fulfill this obligation. In this situation the number of audits could be very high in one year.

It would result in complex bureaucracy in filing and de-filing on the PV SMF as well as for the changes to be included in the logbook without adding value. Additionally, audit findings and CAPAs are not available immediately after an audit. It requires first to write and issue the audit report and then the auditee to suggest CAPAs which then would need acceptance by the auditing group. Therefore 'immediately' seems in fact unrealistic.

A more workable solution for Celgene would be that during the annual or 6 monthly review of the PV SMF, the audit section is updated and open/outstanding CAPAs are addressed and discussed. This would reduce administrative burden without having an effect on the value and accuracy of the PV SMF. The last reviewed versions could be provided upon request of the PV SMF by the competent authority. Improvements of the systems due to closed CAPAs will nevertheless be reflected in the PV SMF revision.

Consultation item no. 4: Should a copy of the audit report be retained in the master file? Would it be appropriate to require documentation of audit schedules?

Celgene believes that a copy of the audit report should not be retained in the master file for several reasons:

- A copy of the audit report in the PV SMF does not add any value as the information regarding main open audit findings are to be listed in the PV SMF.

- It would clearly go beyond the requirements in the legislative text. Art. 104 (2) of Directive 2010/84/EU clearly states that the "MAH shall place a note concerning the main findings of the audit on the PV SMF".
- It ignores the decisions taken by the European Parliament and Council as the proposal to include copies of audits reports in the PV SMF was removed from the legislative text during the legislative process.
- It risks undermining the internal audit process as it has the potential to change how internal documents are written and classified, and make audit reports biased.

On the question regarding the audit schedule, this is a living document requiring vast number of additions and updates. It is not practical to update the PV SMF for each change of the audit schedule or to incorporate a copy of the schedule in the PV SMF that may not be up to date. The schedule could be readily provided during an inspection.

8. Inspection

The requirement to have the PV SMF "immediately" available should be clarified. In PV "immediately" is usually accompanied by "but no later than 24 hours", which might be an option here. In case the PV SMF is held in electronic format, time is required for printing and quality control prior to making the document available to an inspector. This lag time should be considered.

Furthermore, for the sake of clarity we suggest that the text clearly states that the mentioned timeline refers to calendar days (we assume it is the case as we are talking about an EU document), as follows:
"The MAH shall submit the copy of the last reviewed version of the PV SMF at the latest seven **calendar** days after the receipt of the request at its own expenses"

Consultation item no. 5: Overall, do you agree with the requirements as regards the content and maintenance of the pharmacovigilance master file? Please comment.

Overall, yes, but we find that the maintenance requirements and the requirement to have a copy of internal audit reports included in the PV SMF could add unnecessary resource and administrative burdens on the industry, and suggests that the Commission reviews these requirements and clarifies any uncertainties in the text.

B. Quality systems for the performance of pharmacovigilance activities – Common obligations

As a general comment we would recommend that the EMA clarifies pharmacovigilance activities in more detail by i.e. following the current MHRA's Good Pharmacovigilance Practice Guide ('Purple Guide?)[1].

10. Audit

In this section it is suggested that audits of the quality system are performed not less than every two years. The pharmacovigilance quality system is usually covered to quite an extent in every PV audit. Requiring a systems audit of the quality system every two years would to some extend duplicate the efforts by the usual PV audits and on the other hand perhaps delay systems audits of other relevant systems in PV.

We firmly believe that there is no real ground to have a specific audit for quality systems.

C. Quality systems for the performance of pharmacovigilance activities by marketing authorisation holders

13. Resource management

We suggest that a description of what should be included in the PV SMF is specified. We propose the following text:

"The resource management shall be documented in the PV SMF. ***This should include in particular the organizational chart providing the number of people involved in PV activities and showing the split between central and country positions"****.*

13. Compliance management

We propose to change the following sentence as follows:
"(…) To this end, the MAH shall check the European medicines web-portal for any relevant updates, including consultations and notifications of procedures ***on a regular basis****,* ~~*on each working day*~~*."*

Monitoring frequency should be left to the MAH to determine.

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http://www.mhra.gov.uk/Publications/Regulatoryguidance/Medicines/Othermedicinesregulatoryguidance/CON028495

Consultation item no. 6: Is there a need for additional quality procedures, e.g. in relation to study reporting in accordance with Article 107p of the Directive, in relation to communication on pharmacovigilance between the marketing authorisation holder and patients/health professionals; in relation to processes for taking corrective and improvement actions or in relation to the detection of duplicates of suspected adverse reaction reports in the Eudravigilance database?

There is no need for additional quality procedures.

15. Record management

We recommend changing the text as follows:
*"Product related documents **in the PV SMF** shall be retained as long as the **EU/EEA** marketing authorization exists and for further at least 30 years after the MA has ceased to exist".*

The terms "PV system- related documents" and product related documents are very broad. We would recommend giving greater specificity which documents this implementing measure would refer to as per the suggested wording above.

It is also important to clarify that it refers to the EU/EEA marketing authorization. If other MA worldwide were to be considered this would result in different timeframes.

D. Quality systems for the performance of pharmacovigilance activities by national competent authorities and EMA

E. Signal detection and risk identification

20. General

It would be desirable for EMA to notify MAH of any findings from its signal detection on the MAH's product before publicizing any such findings. This would factor in the limitations of drawing conclusions only from a Eudravigilance source and would allow the MAH to provide additional perspectives within a required timeframe.

It is not entirely clear whether access to Eudravigilance database will be granted to MAH to permit signaling on its own products, or to use proportional analyses to compare with all products. We recommend that this question is clarified before there are obligations imposed which might be linked to a future access. We would also recommend that EMA publishes its guidelines on its signal detection methods without delay, to enable transparency for MAHs.

G. Transmission and Submission requirements

Consultation item no. 13: Is there additionally a need for transitional provisions as regards certain aspects of this implementing measure, especially in relation to the specifications on format and content? Please comment.

As the implementing measures will only be available shortly before the new legislation comes into effect, Celgene considers that there will be a need for additional transitional provisions.

Annex II – Risk management plans

Consultation item no. 15: Do you agree with the proposed format and content? Please comment.

In the sentence "where a RMP covers several medicinal products, a separate Part IV shall be provided for each medicinal product", it should be clarified what is meant by "medicinal product". Capsules and tablets could be different medicinal products but have the same administration route and should result in a similar Part IV. Therefore it should be the possibility given that similar administration routes could have a shared Part IV.

1.3 Updates of the Risk Management Plan

If a RMP has previously been submitted for the medicinal product, submission shall be in the form of an update.

It should be possible that due to the modular system only impacted and updated Modules can be submitted for an update instead of a complete RMP with also not-updated Modules incorporated to make the updates faster visible due to lower volume and dilution by not updated documents (i.e. as currently possible for medicinal product dossiers submitted via e-CTD).

Annex III – Electronic periodic safety update reports

Consultation item no. 16: Do you agree with the proposed format and content? Please comment.

It would be useful to have some statements around the required frequency of PSURs and the time at which an automatic annual schedule could enter into force. We want to try and avoid a

situation where the EMA is late with its assessment report on the previous 6 month PSUR and the MAH doesn't know whether it can run with an annual schedule until it is too late. On a similar vane, a timeframe for issuance of a PSUR assessment report by EMA would be useful. If a report is received late, the MAH does not have time to incorporate EMA's requests in the next PSUR. This results in unnecessary work efforts and burden on agency and company site at the moment.

Annex IV – Protocols, abstracts and final study reports for the post-authorisation safety studies

The title should also reflect the scope mentioning:
"Annex IV – Protocols, abstracts and final study reports for **non-interventional** post authorization safety studies"

1. Scope and definitions

We suggest amending point 4. As follows: "End of data collection means the date at which the analytical data set is first **complete** available".

1. Format of the study protocol

In the Format of the study protocol the point "justification for representation of the study population for generalization of results" is missing which is mentioned under final study protocol. This should not be a post-hoc justification as this should be a rationale for the proposed study population.

Regarding point 10 (see text below)

10. Protection of human subjects: Information about whether study subjects will be placed at risk as a result of the study, provisions for maintaining confidentiality of information on study subjects, and potential circumstances and safeguards under which identifiable personal information may be provided to entities outside the study; consideration of the need for submitting the protocol to an Institutional Review Board/Independent Ethics Committee and the requirement of informed consent in accordance with local law.

The specific mention to "Information about whether study subjects will be placed at risk as a result of the study (...)" is not clear as the scope of the study is clearly a **non-interventional** post-authorization study. In such a study design the medicinal product is used according to its approved indication, dose etc.. Therefore, the subjects or patients can't be placed on an additional risk as a results of the study compared to the public health situation for not participating patients as the product is used accordingly to its SmPC.