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PCIM/11/01 – Public Consultation

Concept Paper "Implementing Measures in order to Harmonise the Performance of the Pharmacovigilance Activities Provided in Directive 2001/83/EC and Regulation (EC) No 726/2004" SANCO/D3/FS/cg/ddg1.d.3(2011)1003866

Comments of the European Confederation of Pharmaceutical Entrepreneurs (EUCOPE)

We refer to Directive 2010/84/EU and Regulation (EU) No 1235/2010 which empower the Commission to adopt implementing acts.

The European Confederation of Pharmaceutical Entrepreneurs (EUCOPE, www.eucope.org) was founded to promote companies and associations active in research, development, production and distribution of pharmaceutical products and enhance their scientific, technical, economic and legal objectives. Via the German Pharmaceutical Industry Association BPI with its 270 member companies and the UK pharma association EMIG with its 140 member companies as well as via BioDeutschland with 275 highly innovative biotech companies, EUCOPE represents more than 680 member companies, many of them SMEs. In addition, many innovative companies from Sweden, UK, Bulgaria, Italy, Greece, Germany, the Netherlands and Austria are represented on the board of the association.

I. General remarks

We welcome the legislation by the Commission together with the Parliament and the Council in the field of pharmacovigilance in general. As the Commission pointed out in their concept paper (p. 2), the implementing acts should find the correct balance between safeguarding public health and internal market requirements.

It is highly appreciated that the draft implementing measures are presented in a single paper with the aim to have one harmonized and integrated approach concerning pharmacovigilance activities within the European Union.

EUCOPE would like to draw attention to the challenges of medium-sized companies. Due to the changed definition of the term “adverse reaction” in Directive 2010/84/EC and the changes in the reporting requirements (reporting of non-serious suspected adverse reactions as individual cases) the quantity of data which has to be submitted electronically to the Agency will dramatically increase. This is especially burdensome for smaller and medium-sized companies. In the past a lot of these companies did not need an IT-infrastructure as competent authorities allowed paper submissions for the very limited quantity of ICSRs due to the different definition of adverse reactions.

From our point of view the EU pharmacovigilance system as a whole should follow a risk-based approach with reasonable requirements. It has to be borne in mind that resources of competent authorities and industry are limited. Thus, to fulfill the pharmacovigilance tasks the resources should be allocated in a way that the responsible persons can take care of really important problems and tasks.

Concerning the risk-based approach e.g. the following facts could be taken into account to avoid extended reporting:

- well-established products with well known and overall non-serious adverse reactions, e.g. generics, traditional herbal and other OTC medicinal products,
- generics with a variety of well established products in sum generating a large volume without added value.

For companies producing for example homeopathic medicinal products the range of essential remedies is considerably larger compared to other fields of the pharmaceutical industry. A large number of them have a low to very low turnover. In addition, these companies are holders of several hundreds to more than thousand marketing authorizations.

Therefore, it is of high economic importance for these companies that the regulatory and administrative burden linked to pharmacovigilance is rational, efficient and proportionate as compared to the very low risk profile, i.e. restricted to a minimum, while of course guaranteeing the quality and the safety of the products. It goes without saying that the relevant fees should equally be proportionate.

For industry as a whole and especially for SMEs, a streamlined, clear and efficient pharmacovigilance system, which is not overloaded by purely administrative measures without added value to patient safety, is needed in Europe.

II. Specific Consultation Items

A. Pharmacovigilance system master file (PV SMF)

1. Definition

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

2. Location

In view of the fact that the PV SMF may also be stored/held in electronic form on condition that a clearly arranged printed copy can be made available it should be sufficient that the PV SMF is available at the site where the qualified person responsible operates. The necessity that the PV SMF shall be located at the site where the qualified person responsible for pharmacovigilance operates would not be practical, especially for SMEs.

3. Content

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

Concerning the covering of additional processes and pharmacovigilance tasks, we see no need for further provisions in this respect because all relevant points are already foreseen in the PV SMF.

Looking at Chapter “3. Content” a list of medicinal products relevant to the pharmacovigilance master file should be included from the viewpoint of the Commission. Apart from the fact that such a list will be very extensive the benefit of such a list is questionable especially if a company has only one single PV SMF in place. In any case the information asked for should be strictly limited to what is really needed for the identification of the products: a list of short product names. More detailed information has to be provided in the EudraVigilance Medicinal Products dictionary.

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 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 (see below).

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.

4. Maintenance

As it is stipulated in the concept paper 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 of 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 especially challenging for companies with few employees and in particular for those with a large number of products, such as generic companies. Therefore we are of the opinion that 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 industry. 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 authorization. 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 authorization 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?

We like to point out that an obligation of the MAH to notify significant changes/modifications to the competent authority would lead to additional administrative work and costs. The competent authorities would also have to deal with very high-volumes of data which would be very difficult to monitor. A duty of active notifications would also counteract the aim of avoiding time-consuming variation handling.

A notification of significant changes to the master file to the competent authorities other than for reasons already specifically defined in Article 23 (4)(2) of Directive 2001/83/EC is not necessary and is not asked for by law. As stated in Article 23 of Directive 2001/83/EC and Section 8 (Inspection), national competent authorities and the EMA may at any time ask the MAH to provide a copy of the PV SMF. The MAH shall submit the copy at the latest seven days after the request.

In case such information would be required, the meaning of the term "significant changes/modifications" should be clarified in a strict manner in order to take account of the exceptional nature of the proposed obligation.

5. Documentation

In order the keep the PV SMF legible, as underlined in the concept paper, the documentation should exclude the "logbook" which would be extremely voluminous without offering serviceable or "new" information for the users.

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 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.

6. Delegation

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.

We cannot see any compelling need for being more precise on potential delegation.

Referring to the duty to include copies of the signed agreements with third parties it has to be borne in mind that the number of such agreements is very high and might contain confidential information not related to issues of product-safety. Furthermore, "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. Therefore, the PV SMF should at maximum include a line listing of the existing contractual agreements but no full copies of each agreement. Of course, upon request individual contracts would be made available to the authorities.

7. Audits

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?

A copy of the audit report should not be retained in the PV SMF because such a requirement would be contradictory to the idea of audits/self inspection. Furthermore, it exceeds the scope of Art. 104 (2) and ignores the legislative process of Directive 2010/84/EU which gave up the original proposal of such an obligation. If a copy of the note would have to be retained this would mean the same as if the note itself was retained and therefore contradict the legal obligation to remove the note when the corrective actions have been fully implemented.

Finally, it seems to be appropriate to define the term “immediately”. Such a definition should take into account the complex structure of the factual working process (e.g. time to draw up audit report, involving several affiliates, outsourced pharmacovigilance tasks to multiple vendors, lots of co-marketing products). A more workable solution could 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.

8. Inspections

We see a need to specify the term “immediately” (e.g. “but no later than 24 hours”). It is worth noting that a certain amount of time is required to prepare the copy

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

The PV SMF should allow an overview of the company’s pharmacovigilance system providing information on the key elements. It should not be seen as a depository for the primary data relating to individual elements of the pharmacovigilance system. Taking this into account the extent and detail for some of the individual elements listed in the Concept Paper may contradict the efforts to have an easily-manageable PV SMF providing an effective overview of the company’s pharmacovigilance system.

A useful solution would be to allow cross-references between the PV SMF and the company’s pharmacovigilance system having e. g. the possibility to provide lists (with titles) of core procedural documents or describing MAH-specific data inventories/ systems.

More detailed information can rather be made available on demand, e.g. by the MAH providing detailed standard operating procedures.

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 e.g. following the general and clear structure of the current MHRA's Good Pharmacovigilance Practice Guide ('Purple Guide?)[1].

10. Audit

A requirement for specific audits of the quality system is futile as the pharmacovigilance quality system is usually covered to quite an extent in every pharmacovigilance audit. There is even the risk of delays with regard to other audits which might be more urgent.

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

13. Resource management

Regarding the documentation of the resource management in the PV SMF (see p. (7) (b), (13) of the concept paper) we see a need to clarify which documents are subject to this obligation. We propose to include a limited number of papers (e.g. organizational chart providing the number of people involved in pharmacovigilance activities and showing the split between central and country positions).

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"****.*

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

14. Compliance management

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?

We do not see a need for additional quality procedures. It would be most appropriate for the EMA to detect duplicates of suspected adverse reaction reports in the EudraVigilance database. The obligation for the MAH to "check the European medicines web-portal for any relevant updates, including consultations and notifications of procedures, *on each working day*" seems not to be feasible, especially for SMEs with limited resources. Therefore, the timelines for monitoring the European medicines web-portal should be less strict and appropriate for the individual medicine ("risk based approach"). It should be up to the MAH to define a right "monitoring timetable" because he has the most accurate information and experience regarding his products which enables him to undertake the suitable measures.

If the Commission would regard it as absolutely necessary for MAHs to check the European medicines web-portal on each working day regarding new information it is suggested to have a clearly defined area of the portal where pertinent information will be posted. A system with daily e-mails by EMA concerning new information being posted would be an important tool to help MAHs and especially SMEs.

Independent from the obligation for MAHs to check the European medicines web-portal this should not replace direct correspondence of the competent authorities or the EMA with the MAH on individual product related issues.

15. Record management

The terms "PV system-related documents" and "product-related documents" are very broad. We see the need to provide more clarification as to which documents this implementing measure would refer to and would thus 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".*

Furthermore, it is 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.

Consultation item no. 7: Do you agree with the requirements for marketing authorization holders? Please comment.

The terms “PV system-related documents” and “product-related documents” are too far-reaching and unclear. Record management should also be limited to EU/EEA marketing authorizations in order to avoid legal conflicts. This should be addressed in the Good Vigilance Practice guideline.

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

Consultation item no. 8: Do you agree with the quality system requirements? Please comment, if appropriate separately as regards for marketing authorization holders, national authorities and EMA.

The quality system requirements are agreed in general. In section 10 it is stated that the MAH should perform an audit of their quality systems in regular intervals, not less than every two years. This strict 2-year period for audits is not appropriate as a general rule. A risk-based approach should be followed allowing for longer periods and events-related audits.

MAHs should determine the frequency of their internal audits, based upon information on the performance of the pharmacovigilance system and/or findings arising from ‘routine’ audits conducted on a pre-scheduled basis. However, repetitive ‘routine’ internal audits on a fixed schedule could become a disproportionate effort when compared with the effectiveness of a more ‘risk-based’ approach

E. Signal detection and risk identification

20. General

We would welcome that the EMA would notify the MAH of any findings from its signal detection regarding his products before publishing this information. This would enable the MAH to provide additional information ensuring the quality of the publication.

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.

24. Work sharing of signal management

Consultation item no. 9: For efficiency reasons a 'work sharing' procedure could be appropriate for the monitoring of medicinal products or active substances contained in several medical product. However, do you see a risk in cumulating all tasks (for the authorisation, PSUR scrutiny and EudraVigilance monitoring) in one Member State, as thereby the benefits of parallel monitoring may be lost ("peer review" system)? Additionally, it may be envisaged to extend 'work sharing' to all medicinal products (including all centrally approved products) and to appoint a lead Member State in addition to EMA (Article 28a(1)(c) of Regulation (EC) No 726/2004). Please comment.

The proposed 'work sharing' procedure is supported. The feared risk in accumulating all tasks e. g. for one active substance in one Member State is little. Any Member State would retain the right to comment or conduct additional review if deemed necessary. The work sharing procedure should be extended to all medicinal products which have been approved in more than one EEA country within the EEA. A system of "Rapporteur / Co-Rapporteur" could be envisaged.

Consultation item no. 10: In the Commission's view the aim of this part is to establish common triggers for signal detection; to clarify the respective monitoring roles of marketing authorization holders, national competent authorities and EMA; and to identify how signals are picked up? Are the proposed provision sufficiently clear and transparent or should they be more detailed? If so, which aspects require additional considerations and what should be required? Please comment.

An appropriate level of diversity in signal detection methods should be the aim. No single system or process will yield a perfect result. In this regard, general principles would probably be more useful to establish commonalities than selecting one single methodology to be applied in different settings.

When contemplating methods concerning signal detection it has to be kept in mind that there are medicinal products on the market with a very limited number of adverse reactions. Concerning these products it might be sufficient to evaluate the ICSRs. Therefore a certain method should not be compulsory.

The aim of the common triggers must be to eliminate false negatives (missed signals) and to keep false positives to a minimum. Thus there is merit in ensuring that the roles of MAHs, national competent authorities and EMA are clarified. Whilst the proposals are clear concerning the role of EMA, a series of process outlines and specific deliverables must be defined for MAHs and national competent authorities in the Good Vigilance Practice guideline.

F. Use of terminology

27. Use of internationally agreed terminology
Consultation item no. 11: Do you agree with the proposed terminology? Please comment.

In general we agree with the proposed terminology.

The specific aspects of homeopathic medicinal products should be duly taken into account. Also, for SMEs and other companies with only a limited number of ICSRs the fulfillment of all requested IT requirements would not be proportionate. Certain (exception) provisions for that must be in place.

A change in terminology goes hand in hand with an additional workload for pharmaceutical companies. Especially for SMEs this is a heavy burden. Taking this into account a transition period for adjustment, at least 5 years, should be foreseen.

28. Use of internationally agreed formats and standards

Consultation item no. 12: Do you agree with the list of internationally agreed formats and standards? Please comment.

The list of internationally agreed formats and standards is agreed, with the exception of item (a) relating to the new Extended EudraVigilance Medicinal Product Report Message (XEVPRM). As discussed at the EMA Stakeholder Meeting on 20 September 2011 a certain amount of data that has to be submitted to EudraVigilance by 1 July 2012 in order to comply with Article 57(2) of Regulation (EC) No 726/2004, as amended by Regulation 1235/2010, goes beyond what is required by law. EUCOPE has addressed the concerns of our member companies in this meeting and in a letter to the EMA. The extent and scope of data required for submission, as it is described in the EMA Legal Notice of the 1st of July 2011 and follow up communication in September 2011, goes beyond the legal basis.

EUCOPE urges the Commission and the EMA to continue the dialogue with industry about the mandatory and non-mandatory information and data fields which have to be provided by the companies in order to comply with Article 57(2) of Regulation (EC) No 726/2004 by the July 2012 deadline.

In any case a proper protection, including a limitation of public access, i.a. by competitors, to certain data, in particular details on the QPPV, must be ensured.

The aim should be to allow the Agency the fulfillment of its pharmacovigilance tasks by submitting really necessary pharmacovigilance related information about medicinal products. All information that is not directly related to this task should be not mandatory especially all information that is related to the ISO IDMP projects. Under the prerequisite that the legal basis is clear the IDMP related information could be included into the system at a later stage when the ISO process is finished.

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.

We definitely believe that there is a need for transitional provisions because the implementing acts will only be available shortly before the new legislative measures come into effect. It is worth noting that a change in format and content does not only influence the document itself but also technical infrastructure, e.g. databases. The technical roll-out of these changes is time consuming.

Especially in relation to PSURs and RMPs transitional measures co-coordinated across the EEA will be necessary. The transitional measures should allow using those processes existing for as long as necessary. In addition, different transition specifications by country or region should be avoided. Regarding the requested time frames for the implementing measures it should be borne in mind that the changes will especially affect SME.

Annex I – Electronic submissions of suspected adverse reactions

Consultation item no. 14: Do you agree with the proposed format and content? Please comment.

The proposed format and content is agreed in general. However, the proposed definitions for ‘misuse’, ‘medication error’ and ‘overdose’ should be clearer. It is challenging to find clear and distinguished definitions for the first two terms, as they may be interrelated. Particularly a more elaborate interpretation/definition of ‘off-label use’ would be of value – as off-label use may be a justified scientifically sound treatment and does not need to be put necessarily into a negative context, where "mis"use clearly implies an incorrect, potentially adverse, situation. Currently it would not be clear whether ‘off-label use’ is covered by ‘misuse’ or whether ‘misuse’ should be considered as part of ‘off-label use’ (important given that PSURs and Risk Management Plans require summarization of ‘off-label use’ rather than ‘misuse’).

The need to send copies of literature should be modified in a way that copies of literature should only be sent upon request. As the case narrative already contains the relevant information, the addition of such copies would constitute an additional burden without any practical benefit.

Annex II – Risk management plans

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

We would like to highlight that the sentence “where a RMP covers several medicinal products, a separate Part IV shall be provided for each medicinal product” should be clarified. It is not clear 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. Thus, there should be the possibility given that similar administration routes could have a shared Part IV.

Although the format and content for products with new active ingredients is agreed in general, in section 1.2 “Format of the RMP” it should be clarified that only the summary of the RMP has to be published on the authorities’ websites. At the moment it could be understood that the full RMP should be published – that would cause problems concerning confidential data.

RMP are also regularly submitted with marketing authorizations applications across the world and international Safety Departments suffer from adapting to various formats already. Thus the EMA shall not further increase this burden.

In this context we would like to point out that risk management plans have not been required so far in case of very favourable safety profiles of specific products. Within Europe the possibility to submit “waivers” has for a long time been broadly accepted in such cases. Therefore this possibility should be maintained. Thus, any changes of the formats should not affect this possibility.

It should be made clear that medicinal products that have a low risk profile or a well-established active substance where no risk minimization measures are necessary “routine pharmacovigilance” is possible. Concerning those medicinal products that build up a very big part of the whole market the format of the RMP should be adjusted following a risk-based approach. Additional bureaucracy that does not lead to a relevant improvement of patient safety should be avoided.

Regarding section 1.3 “Updates of the Risk Management Plan” we would suggest that 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.

We see a need for a clarifying statement about the required frequency of PSURs and the time at which an automatic annual schedule could enter into force. There is a danger that the EMA could be late with its assessment report on the previous 6 month PSUR and the MAH doesn’t know whether he can perform with an annual schedule until it is too late.

A timeframe for issuance of a PSUR assessment report by EMA would also 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.

Additionally, we would like to mention that not all of the listed items are applicable for specific product categories, in particular those products which are based on bibliographic data (e. g. herbal and homeopathic medicinal products).

Finally, we would like to point to the fact that PSURs are often submitted to regulatory authorities outside the EU as well. Format and content should be in accordance with ICH E2C (R2). The timeline for finalization of this guideline will be after the implementation date of the pharmacovigilance legislation, but the alignment of the implementation measure with the ICH E2C (R2) outcome should be envisaged.

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

Consultation item no. 17: Do you agree with the proposed format? Please comment

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

It has to become clearer that there are different requirements concerning studies that have to be GCP-compliant (interventional studies) and those PASS that are non-interventional.

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”. Regarding point 5: „*study protocol*“ is a definition stemming from GCP. The term “observational plan“ would be better to distinguish PASS from GCP studies.

2. 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 an ex-post justification as this should be a rationale for the proposed study population.

Point 3: The naming of the main author of the protocol is not necessary, a principal investigator and co-investigator are not part of all NIS. It should be avoided to use terminology stemming from clinical trials. This is again the character of NIS. The doctor taking part in an NIS does not take part in a clinical trial, he or she treats patients in a way he/she would do in normal daily practice. He/she then documents the results of the therapy (e. g. ADRs, outcome etc.).

Point 4: Naming of main author is not necessary.

Point 7: It is agreed to provide a description of the actual safety profile and an explanation what the aims of the NIS are. All other information go beyond what is necessary. In addition this information has to be shown in the context of the marketing authorization procedure.

Point 8: All NIS mentioned in Annex I are asked for by competent authorities. Having this in mind it would be logical that the competent authority in question should give the reason for conducting the NIS and not the MAH.

Point 9: 9.1 to 9.9: Again it should be made clear that these points are too much related to requirements in the context of GCP. It might be that this is not intended, but the wording implies very complex answers having the GCP system in mind. Hence the wording should be reviewed in this regard or it should be made clear that the distinction between GCP-compliant clinical trials and NIS is seen and the answers can be kept short and simple.

Point 10 (see text below)

The specific phrase “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 result of the study compared to the public health situation for not participating patients as the product is used according to its SmPC.

3. Format of the abstract of the final study report / 4. Format of the final study report

Again it should be made clearer that there is a distinction between NIS and clinical trials in accordance with GCP.

A PASS as a non-interventional study has to reflect the medical routine and reality. Hence, it is not possible with a prospective NIS to look over the doctor’s shoulder on the one hand and to expect data in GCP quality on the other hand.

We remain at your disposal for any questions and would be delighted to discuss the issue in further detail.

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