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Comments on the Draft legislative proposals to strengthen and rationalise the EU system of Pharmacovigilance

GENERAL COMMENTS:

AESGP represents the manufacturers of non-prescription medicines in Europe.

AESGP welcomes many of the Commission's proposals as they would reduce the current administrative burden resulting from duplicative requirements whilst strengthening public health. In particular, we very much support the proportionality of the requirements for medicines with well-known substances in application of the Better Regulation principles.

While the overall objectives of the strategy – striving for clear roles, harmonising requirements, rationalising the processes in order to be able to focus on the most important topics – are appreciated and welcomed, a general concern is based on the fact that the proposed changes are planned to be implemented in part by an update of Directive 2001/83/EC. In order for these proposals to serve their intended purpose of rationalisation and simplification, **there is a need for a more consistent transposition and implementation** of the amended Directive across all Member States. With this in mind, we appreciate any follow-up measures whose goal is to maintain harmonisation in practice.

The proposals present important changes to the way pharmacovigilance is run and enforced. In order to facilitate implementation and create mutual understanding on these new requirements, we recommend that pan-European joint industry-competent authority training sessions are carried out shortly after publication of the new legislation.

DETAILED COMMENTS

I. EMEA Pharmacovigilance Committee (Articles 57(1)(c), 101a to 101l, Article 61 of Regulation 726/2004)

We can see the merit of a Pharmacovigilance Committee that would replace the informal Pharmacovigilance Working Party; this underpins the importance of pharmacovigilance as a key means to protect patient safety. We understand that the new Committee would take on a number of tasks which are currently the responsibility of the Member States. However, **any decision related to a medicinal product needs to be based on a risk/benefit evaluation and cannot cover risk related aspects alone.** This should be kept in mind when deciding on the establishment of such a stand-alone committee and its potential tasks and responsibilities.

The proposal envisages that the Committee would be responsible for a wide range of pharmacovigilance tasks, and we are concerned that the widespread roles and responsibilities of this Committee could result in new administrative burdens and entail significant fees.

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a. Particular concerns/key issues with regard to the wide range of tasks and responsibilities

- The profile of tasks and responsibilities would create an enormous workload for the Pharmacovigilance Committee which could result in potential delays in the relevant decision making processes (e.g. referrals) which would be counterproductive to the goal of streamlining procedures.
- The right to appeal by Marketing Authorisation Holders (MAHs) needs to be included in the concept.
- MAHs concerned need to be consulted before the publication of study results and the implementation of recommendations.
- The criteria for the Committee/ Competent Authority to request additional PSUR submissions, risk-management plans or additional studies (Post authorisation safety studies or non-interventional studies) need to be clearly stated in the Directive (cf. comment section on PSUR and PASS). This is particularly important in relation to non-prescription medicines where a large number of companies may hold marketing authorisations for the ingredient concerned. Hence, no particular MAH could be expected to bear the entire cost of any such required actions and coordination of work effort would be extremely complex.
- We would like to stress the importance for the Committee of having the expertise to review and provide recommendations on a wide spectrum of substances and medicines, including non-prescription medicines. This could be done via cooptation of experts.

b. Referral (Article 101k)

We can see the rationale for the Commission's analysis that *"the existing ´Pharmacovigilance Working Party´ at the EMEA informally discusses important safety issues but its conclusions are frequently not implemented and certainly not implemented comprehensively across all Member States (as they are not legally binding on the Member States or companies). This leads to divergent safety action by the Member States which represents a weakness of public health protection, creates obstacles for the single market and is costly for the industry."*

The Commission states that *"current legal provisions on referrals are unclear and overlapping and the use of the provisions is limited."* Although, AESGP does not quite agree with this statement in general, recent episodes of pharmacovigilance issues discussed in the Pharmacovigilance Working Party have shown the need for improvement. The Pharmacovigilance Committee may remedy this problem by providing one opinion which will lead to a binding decision by the Commission and consistent implementation across Europe.

We appreciate the consideration that one possible recommendation of the new Pharmacovigilance Committee may be that *"no further evaluation or action is required at Community level"* (Article 101k(10)(a)). The experience gathered in the past 12 years has shown that such a conclusion could be reached.

However, AESGP is **not in favour** of the proposal made in section 7 of Article 101k concerning the holding of **public hearings** on referrals. We feel that this would not be an appropriate forum to discuss highly complex scientific and pharmacovigilance issues. Therefore we propose that the standard would be a non-public hearing (following Article 101k section 8), and that only in extraordinary situations (which need to be carefully defined in the Directive), a public hearing would be held.

Furthermore, the **MAH's right to appeal** the opinion of the Committee **is missing** here although it is mentioned in Article 32(4).

MAH(s) should be allowed to review the opinion before it is made public.

II. Good Vigilance Practices (Article 101b)

The development of Commission guidance defining 'good vigilance practices' is appreciated provided that it is proportionate and does not lead to additional burdens, in particular for well known substances often used in non-prescription medicines. Therefore, it **should replace the current Volume 9a and not overlap with it**. It is desirable that such Commission guidance provide clear interpretation and lead to a **harmonised implementation across Europe**.

III. Pharmacovigilance master file (Articles 1(34), 8(3)(ia), 23 and 101l)

We appreciate the proposal that **a Pharmacovigilance Master File should replace the regular submission of the entire "Detailed Description of Pharmacovigilance System".** According to the proposal, submission of key elements of the pharmacovigilance system (i.e. Qualified person for Pharmacovigilance details and statement and site of the Pharmacovigilance system master file) as part of the dossier, will be sufficient. On this matter, we would prefer that Article 8(3)(ia) talks about 'key elements' rather than 'summary' as the latter may imply further work rather than the mere provision of the main elements described above.

However, any changes to this key information are currently subject to a type II variation. We would like to propose that any changes to this type of information be made via notification of the competent authority or that such information be available in the EMEA database/repository which would be accessible by the national competent authorities and easily 'updatable' by the company whenever there is a change.

In addition, this requirement seems to be overlapping with the requirement of Article 101l(4)(a) which states that the '*name and contact details of the qualified person shall be notified to the competent authority and the agency'*. We think that the database / repository mentioned above would take care of this requirement.

Internal Audit reports are seen as internal confidential documents and therefore we are opposed to making them part of the Pharmacovigilance System Master File.

To avoid misunderstandings and confusion, we propose using a standardised wording throughout the text with regard to the pharmacovigilance system i.e. either "Detailed Description of the Pharmacovigilance System" or "Pharmacovigilance System Master File". These expressions are now used as synonyms.

IV. Risk Management planning (Articles 1(33), 8(3)(iaa), 21(1), 21(4), 101i(d), 101p)

One of the key changes to EU legislation is a strengthening of the legal requirement to submit a risk management plan (RMP) at the time of the marketing authorisation application.

We appreciate the **rationalisation of risk management planning** and the fact that "*the risk management system shall be proportionate to the identified and potential risks taking into consideration the information available on the medicinal product*". We recommend that **the specific safety profile and usually long experience in use of non-prescription medicines be borne in mind**. The consultation paper even seems to indicate under 3.2.7 that there need not be a risk management plan for well-established products.

The set-up of a RMP would result in great efforts on the part of the company. Therefore AESGP recommends that the provisions under which such a plan would be required for existing products, would be clearly stated in the Directive. We propose that this requirement should only be triggered by *serious* concerns which may alter the risk-benefit balance.

The expected added scientific value should be balanced against the corresponding costs. We recommend that the above suggestion be clearly reflected in the legislative text.

In addition, for products authorised in more than one Member State and/or with more than one MAH, different national requirements for the RMP should be avoided and ought to be harmonised by the Pharmacovigilance Committee fully taking into account the Better Regulation principles. Article 101p should be modified accordingly.

Risk Management Plans normally include extremely technical and detailed information which we doubt could be of benefit for the public but could on the other hand be of great interest to the competition. **We therefore object to their publication**. In accordance with the proposal for modification of Article 21, the assessment reports would already include elements of the risk management system, which should, provided they are drafted in lay language and put into context, be of more benefit for the public (cf. our comment under Section VII).

Both RMP (Risk Management Plan) and RMS (Risk Management System) are used interchangeably in the Commission's proposals. We propose using RMP throughout the legislation to avoid misunderstandings. Another reason for this proposal is that the abbreviation "RMS" is frequently used for "Reference Member State". Consequently, we propose that the newly defined term "Risk Management System (RMS)" (definition in Article 1(33)) be replaced by "Risk Management Plan (RMP)".

V. Oversight of non-interventional safety studies (Articles 1(15), 101g, 101h, 101i(h))

Key proposed changes of the legislation include the introduction of a legal basis for post-authorisation safety studies (PASS) and non-interventional safety studies (NISS) after granting of the marketing authorisation.

Post-authorisation safety studies (PASS):
PASS could be a very efficient tool to clarify potential risks of medicinal products but we object to the broadening of the definition (in Article 1(15)) which makes the scope of potential studies unclear.

We support the fact that serious concerns would need to be justified to motivate such requests. Those serious concerns would need to be defined.

We recommend extending the MAH comment period and including the rights for industry to appeal against recommendations of the competent authority. In case of appeal by the applicant, the matter should be referred to the Pharmacovigilance Committee for an opinion.

In addition, for products authorised in more than one Member State and/or with more than one MAH, different national requirements for PASS should be avoided. We suggest that the applicant be given the possibility to bring the issue before the Pharmacovigilance Committee for an opinion.
Careful coordination of such activities would be required to avoid multiple MAH independently conducting the same study and to ensure that all MAHs share responsibility for such efforts.

Non-interventional safety studies (NISS):
The proposed timeline of 60 days in which the competent authorities are allowed to respond to the submission of a non-interventional study is regarded as too long.

The requirement to submit an abstract to the Committee in addition to study reports and in addition to the general requirements on the submission of trial results seems to be superfluous.

If this requirement is maintained, the MAH should be consulted before publication of the abstract of the study results on the web-portal.

VI. Reporting of single serious adverse drug reaction (ADR) case reports

a. Expedited Reporting Requirements (Article 101e)

We concur with the analysis of the Commission that *"the current ADR reporting rules are very complex and lead to heavy costs on industry and regulators. There is a major scope for simplification by eradicating unnecessary duplication of reporting […]."*

We appreciate that the **assessment of expectedness** which poses an enormous burden for multinational companies **should no longer be relevant for submissions of Individual Case Safety Reports (ICSRs).** In addition, we agree to submission of all serious cases in an expedited manner (within 15 days) as it was proposed for non-EU-cases.

However, we **cannot see the added value of expedited submission of all ICSRs that occurred within the EU** (even the non-serious ones). Non-serious reports are often well known to physicians, MAHs and Competent Authorities, and they are much more frequent than serious reports. The relation is often 1 serious report to 10-20 (or more) non-serious reports. This ratio will be even higher for well characterised non-prescription medicines where virtually all reports are non-serious.

In order to comply with the proposed expedited reporting requirements companies will have to increase their human resources to ensure an immediate data entry into their databases of all adverse reactions reports. This would be completely counterproductive to the objective of the Commission proposal to free up resources and to reduce bureaucratic burdens for industry. In relation to these enormous efforts the added value of non-serious reports for pharmacovigilance purposes, e.g. for signal detection, is quite limited. On the contrary, high numbers of not necessarily relevant non-serious expected reports might dilute important pharmacovigilance signals.

Taking into account the fact that enquiries to healthcare professionals are necessary to validate consumer reports, AESGP would like to propose a **prolonged reporting period for non-serious reports of 90 days.** This would result in more consolidated reports, and a significant reduction in the number of follow-up reports; therefore enormous resources could be saved for both the industry and the EMEA.

In section 1 of Article 101e, it is mentioned that "The MAH shall accept reports of adverse reactions electronically". Does 'electronically' mean that reports should be submitted by competent authorities/MAHs using a E2B compliant database or by consumers/healthcare professionals via email?

b. Literature Screening (Article 101e(5))

AESGP very much appreciates this proposal as it has always been a proponent of simplification of this procedure to avoid duplicate reporting of literature cases for active ingredients with a well established safety profile.

We would like to mention that a guide is being created by the "Simplification of ADR reporting for worldwide Literature" subgroup of the EudraVigilance Expert Working Group (EV-EWG).

Based on the experience of its German member association, AESGP takes the freedom of providing advice pertaining to the conduct of medical literature monitoring in the enclosed Annex 1.

In addition, it warns that the screening of literature will require a number of resources and this task alone would take up a major part of the EMEA's resources dedicated to pharmacovigilance. Outsourcing this literature service to a qualified CRO could be a solution to lessen the EMEA's workload. A prerequisite would be that a fixed protocol between the CRO and the EMEA is developed under defined contractual terms and agreed by all stakeholders.

MAHs are fully responsible for their products. This includes the duty to screen the literature worldwide for new information about the safety profile of their products. **It should be made clear that the tasks performed by the EMEA (or on its behalf by a contractual agreement) waive the need for the MAH to do so**. This is crucial from a liability perspective.

Alternatively, the following information should to be made available so that companies can decide whether the literature scanning by the EMEA fulfils the company's regulatory obligation:

- List of substances for which literature is scanned for
- List of journals or databases (e.g. medline, EMbase, etc.) that would be scanned
- Details of validated process for identification of Adverse events reports
- Timelines by which the literature will be available on Eudravigilance for industry to access and to fulfil its regulatory requirements in other countries (e.g. the US)

In light of the centralisation of literature scanning, **no additional queries** in relation to literature search should be raised by EMEA and/or Member States to the MAHs.

In addition, some other important issues remain unclear in the current proposal:

- Should it be mandatory for all MAHs in the EU to participate in the screening?
- What is intended regarding the funding of this service?
- For a proper assessment of findings regarding, for example, herbal substances and preparations, special expertise is necessary. How it is intended to deal with this issue?

c. PSURs (Article 101f)

AESGP is very much in favour of the exemption regarding the PSUR preparation for substances with well-established safety profile.
This concept should by analogy be applied to all medicines which have been on the market for at least 10 years and which have non-prescription status. **Concretely, we would like this PSUR exemption clause to cover well-known medicines which were put on the market prior to the creation of the 'bibliographic application' (Article 10a) and which do not meet the criteria listed in Article 71 of Directive 2001/83/EC as amended.**

We agree that is it reasonable to focus efforts on the preparation of PSUR for new substances.

It is stated in Article 101f(2) that *"reports shall be submitted electronically"*. But it remains unclear what is intended by 'electronically' as there is no internationally agreed structure and format for electronic submission of PSURs (contrary to Individual Case Safety Reports (E2B-M2)).

Considering that - following the Commission's proposal - all serious case reports from third countries and all reports (serious and non-serious) that occurred within the EU should be submitted immediately to the EudraVigilance system, a re-submission of reports or line listings seems to be inappropriate and redundant and should be avoided. Therefore, we generally agree with the following statement in Article 101f(1) in the Commission paper: *"Periodic safety update reports shall present summaries of data relevant to the benefits and risks of the medicinal product and shall not routinely contain listings of individual case reports already submitted to Eudravigilance."* We would recommend taking out the word 'routinely' in order to avoid any misinterpretation.

It should be clarified if the PSURs should be electronic versions of the remaining summaries of data – i.e. text files - or whether another format would be required.

In general we agree that the concept of PSUR work sharing, together with the EU Harmonised Birth Dates (EU HBDs) will be included in the Directive as it is a useful concept to save resources for both industry and regulatory authorities as well. However, it should be clarified that the use of EU HBDs by the MAH remains voluntary.

Article 101f(4)(d): we recommend that a request for a PSUR for products normally covered by the exemption clause be accompanied by a detailed justification.

Regarding the publication of the assessment and the results of the PSURs, we refer to our comments under Section IX.

d. Consumer Reports (Article 101e)

In principle, we support the concept of empowerment of patients/consumers in pharmacovigilance and in particular in the reporting of potential adverse drug reactions to industry.

However, we fear that, as previously observed and reported in literature, the system may be overwhelmed with reports of minor symptoms and cases where the patient is unable to discriminate effectively between symptoms attributable to individual drugs or diseases. Hence regulatory agencies may find signals of new Adverse Drug Reactions (ADRs) harder to spot in the "noise" of patient reports. A significant volume of ADR reports will also have economic consequences in terms of the resources required for analysis. Patient reports are likely to be stimulated by media reports which may bias signal generation processes.
Therefore, the reporting system needs to have structures in place in order to avoid reporting bias which may affect the functioning of the system in general. The reporting system would need a proper evaluation.

In addition, little experience can be drawn from Member States, as patient reporting is only practised in the United Kingdom (since 2005), the Netherlands and Denmark.

Therefore, as such, the reporting system may lead to an increased workload for the authorities and industry. **We doubt that it will add value in practice.**

In order to have a proportionate and workable system, we would suggest the following:

- In order to facilitate the evaluation of a causal relationship, the MAH needs the healthcare professional's contact details (physician or pharmacist for non-prescription medicines). Therefore, the reporting form template should call for complete contact information of the physician and/or pharmacist, the rationale for providing such information and a statement reassuring patients of the confidential handling of the data provided.

- Filling out the healthcare professional's information should be encouraged. If the ADR cannot be medically confirmed, the company would record it but would not need to report it to the EudraVigilance.

In accordance with section 1, MAHs should record all ADRs which are brought to their attention and report those where a causal relationship is deemed reasonable. However, the establishment of a causal relationship proposed in point (b) is based on a number of factors. Temporal relationship plays an important role; however, a mere temporal association should not automatically lead to the assignment of causality.

In section 3, the national authorities will record all ADRs from patients and submit them electronically to EudraVigilance and to the MAH. In case patients report directly to authorities' websites, will it be the tasks of the MAH to collect this information from those websites? The reporting flows need to be structured in an unambiguous way in order to avoid duplicate and parallel reporting.

It also remains unclear why reports for drugs on the intensively modified list should go to the MAH directly (cf. Article 59(1)(ba)) whereas all others should be channelled to the national authority. Again, the interaction between the MAH and the national authority needs to be clearly structured to ensure that all parties have access to the full information and that the reporting pathways to EudraVigilance are clear in order to limit multiplication of efforts and omissions.

Paragraph 3 of section 3 refers to "national competent authorities for patient safety" and "national competent authorities for medicinal products". Which entities are these terms referring to?

In the public consultation document (under section 3.2.6, page 7-8), the text should be made consistent and mention 'Adverse drug reactions' instead of 'side effects.'

VII. Medicines safety transparency and communication (Articles 21, 23 and 101i)

Strengthening of medicines safety transparency and communication is among the main changes introduced by the Commission proposal.

AESGP appreciates any efforts to coordinate and to harmonise communications from the Member States regarding safety issues. However, the respective **MAHs should be kept informed of content and time of release prior to the actual publication on the website**.

With regard to the intended publication of study protocols we cannot see any added value from a pharmacovigilance point of view. On the contrary those protocols may contain highly confidential information of major competitive value. **To avoid any negative implications, the publication of study protocols should be deleted from the concept.**

Assessment reports will include elements of the risk management system which will be made publicly accessible. Communication related to risk management system needs to include appropriate language and context for public understanding. Companies need to be consulted before this type of information is made public.

It is also intended to post a **list of the qualified persons for pharmacovigilance** on the web portal. It is critical that the access to this information is strictly limited to the authorities and controlled so as to **help prevent misuse and inappropriate handling of this information**. This should also respect the national legislations on data privacy/protection. **We therefore strongly object to making such information publicly available.**

Moreover clarification is needed as to who will be responsible for the accuracy and maintenance of the data published on the web portal. According to Article 23, the MAH should ensure that the product information reflects the current scientific knowledge as well as recommendations published via the EU Web Portal.

VIII. Clearer safety warnings

Key Safety Information (Articles 11(1)(3b) and 59(1)(ba))

The Commission proposes the addition of "key safety information about the medicinal product and how to minimise risks" about the medicinal product in a box surrounded by a black border in the Summary of Product Characteristics and Patient leaflet.

In the accompanying Commission consultation paper it is foreseen that this provision would have to be complied with within a 5-year transitional phase (i.e. at the time of the next renewal or in conjunction with the next major variation). The legislator foresees that the implementation cost would be minimal.

Firstly, and in the absence of any defining criteria, we wonder what this 'key safety information' would be. If maintained, this should be defined so as not to allow divergent interpretations.

The benefit for such a new section consisting of a repetition of information already present in other sections of the product information is questionable. It is expected that the patient would focus on this information and neglect the information in other sections of the leaflet. More importantly**, putting the emphasis only on the risk of taking the medicine and not balancing it with the risk of *not* taking the medicine may unduly frighten the patient** and deter him/her from taking the medicine. Especially for the patient information leaflets which were proved valid, appropriate and comprehensible by patients' consultation, no further safety information should be needed. On the contrary, redundant presentation of risk information **may adversely affect compliance**. Patients might interpret the messages in a black box not in the sense that these events *may* occur but that they *will* occur. This in turn may present a safety issue (non-treatment of potentially significant disease).

In addition, the black box may give the impression that new safety information has been added which would mislead the patient.

We question the assumption that the implementation costs of this proposal would be minimal. For the majority of the products on the EU market, no further renewal will take place. Therefore, a variation would be needed which would give rise to additional efforts and fees.

The feasibility of adding additional language on already long leaflets should also be assessed. One may also wonder whether this addition will trigger a readability testing on this specific key information.

Another issue is that for nationally authorised/registered products, the key safety information needs to be discussed with each national competent authority which may result in inconsistencies and require a lot of efforts. Coordination would be needed so as to avoid such a situation.

The benefit of this proposal is questionable, in particular for well-known medicines, and will bear a non-negligible cost. Thus, and for the reasons presented above, this proposal seems contrary to the 'better regulation principles' and by consequence, **AESGP recommends deleting it.**

In case this measure is maintained, the 5-year transitional phase mentioned in the consultation paper should be reflected in the draft proposal and start from the implementation date.

IX. Other comments

Update of product information (Article 23)
The handling of variations is a process with a great deal of interdependencies. If new safety data have to be implemented in all SPCs in a fast and timely fashion, the rules for handling of variations need to allow for this. The new variations guideline should plan for this.

Pharmacovigilance activities and fees (Article 101c)
Fees should be proportionate to the amount of work to be carried out.

Supervisory authority for inspection (Article 101l and amended Article 18 of Regulation 726/2004)
We appreciate the introduction of such a measure which would reduce inspections by several Member States. However, we would appreciate more flexibility i.e. the country supervisory authority should not necessarily be linked with the location of the Qualified Person for Pharmacovigilance. This issue could be negotiated in the context of the authorisation procedure. In general, the Member State which was the (co)-rapporteur in the centralised procedure should be selected as it will have the necessary means and knowledge to carry out this responsibility.

Responsibilities of the MAH (Article 101l(4))
In order for the MAH to be able to monitor the data on EudraVigilance for signals, the relevant personnel as well as the QPPV should be given access to the EudraVigilance database

Provision of ADRs reports to the public (Article 101d(3)):
We question the intended benefit of this provision.

Responsibilities of Member States (Article 101l(2)):
We appreciate the pragmatism shown here which allows a Member State with fewer resources to delegate its tasks to another Member State. We recommend that the concerned MAHs are informed.

Collation of reports (Article 101e(1))
The sentence "*these reports shall be collated at one point within the Community*" should be explicated or deleted as, as such, it does not add anything in the way it is currently phrased.

Article 117(3): We think that this clause lacks clarity.

Article 57(2) of Regulation 726/2004: The transition period of 18 months may be too short for smaller companies. Some flexibility should be given.

Annex 1: Prerequisites for an efficient literature screening

Service Provider:

- Transparent process for identification and selection of potential service provider
- Definition of a call for tender
- High reliability of the body which performs the literature screening service (e.g. widespread expertise regarding chemically defined active ingredients and actives of special therapies and long-term experience in literature screening)

Service:

- Inclusion of all active ingredients of medicinal products authorised or registered in one or more Member States of the European Economic Area
- Transparency of the service, regarding e.g.,
    - search criteria
    - frequency of screening
    - criteria for the assessment of the hits identified
    - tools for information exchange with the respective MAHs
    - detailed description of processes and procedures by (public) SOPs and/or working instructions.
- Use of validated tools and software, e.g. for screening and signal detection, accessible by the MAHs
- Ability to be audited by the MAHs
- Ability to download reports (E2B compliant XML files) for reporting to other competent authorities
- Ability to generate line listings e.g. for PSUR preparation
- Monitoring and maintenance of the service by a committee with adequate representation of industry, e.g. the EudraVigilance Expert Working Group or one of its subgroups

Financing:

- Implementation of a transparent and fair concept for financing of the service

Brussels, 4 February 2008