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AESGP response to the Commission's Public Consultation: Assessment of the Community System of Pharmacovigilance

AESGP welcomes the Commission's consultation on the assessment of the Community Pharmacovigilance system. We appreciate the opportunity to express our views and experience on the current pharmacovigilance system and to make proposals with regard to the implementation of legal provisions in this respect.

GENERAL COMMENTS

Characteristics of non-prescription medicines

AESGP represents the manufacturers of non-prescription medicines in Europe. Non-prescription medicines (defined by default in Article 72 of Directive 2001/83/EC as amended) are "*medicinal products which do not meet the criteria listed in Article 71*", namely, those products are unlikely to present a danger either directly or indirectly and are deemed safe enough to be used without prescription and medical supervision. **Non-prescription medicines are in most cases well-established medicines with recognised efficacy and an acceptable level of safety which have been on the market for 10 years or more**. Their safety profile is well-known due to their long-term experience and widespread use.

Many manufacturers of non-prescription medicines are small and medium sized-enterprises (SMEs).

Differentiation between substances

The current legislation applies to all categories of medicines in an equal manner, whether the medicine is a new chemical entity which has been recently approved and launched on the market or an 'old' substance which has been used for years.

We believe that there should be some kind of differentiation in the requirements according to the type of medicine and the level of knowledge acquired on its safety profile over the years.

This was also amongst the recommendations put forward in the Fraunhofer study which stated that "***it should be distinguished between new and other drugs […] on the one hand, and "old" and well-known drugs […]***" (p.166) and that ***"it should be identified how the requirements can be made as supportive as possible"*** (p.170).

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New legislation versus harmonised and consistent implementation

The recently amended pharmaceutical legislation includes the legal requirements in relation to pharmacovigilance. These are further explained through a number of guidance documents.

While improvements to the existing legislation are always possible, we believe that the best should be made out of the recently modified pharmaceutical legislation which was agreed upon after an intense political debate. We believe that **'a new legislation' would not necessarily obtain better results but would create a period of uncertainty - at least for a couple of years - without any guarantee of a better system.** We would rather suggest making the best of the current system and focusing on a risk-based application of the requirements at Community and national level. At national level, consistent approaches should be reached through benchmarking, and/or the sharing and application of best practices between Member States. This aspect was also put forward by the Heads of Agencies in their strategy document[1].

At this point in time we believe that it is necessary to focus on an appropriate implementation of the legal requirements. The current revision of Volume 9a of the Notice to Applicants seems to be the appropriate setting for interpreting the legislation and providing clarifications. We believe that many problematic issues could already be solved by amending this document.

Work-sharing concept

We fully concur with the recommendation put forward by the Heads of Agencies in their Strategy report[1] to "***optimise the utilisation of scarce resources by fully implementing established work-sharing concepts and by identifying additional fields of work-sharing*".** This would be of particular interest and benefit for small and medium-sized enterprises. This point is further developed in the second part of this paper.

Use of EudraVigilance database

Continuing to send case reports to all competent authorities is not in line with the purpose of this database and will make a successful operation difficult. For example, unexpected serious adverse reactions occurring outside the EU should be sent only to one authority and be made available to all the others via the EudraVigilance database. This would save time and resources to both competent authorities and industry. This point should be addressed within Volume 9a of the Notice to Applicants.

Pro-active pharmacovigilance

We think that the requirement to describe the pharmacovigilance system (and, where appropriate, the risk management) within a pharmaceutical company may provide the opportunity for a more pro-active pharmacovigilance. This would provide the competent authorities with reassurance that an appropriate system is in place and therefore would eliminate the need to submit data on a routine basis for administrative purposes. It should be possible to submit the description of pharmacovigilance once per Marketing Authorisation Holder (MAH) per category of products (e.g., well-know medicines).

[1] Heads of Medicines Agencies Strategy for the European Medicines Regulatory Network – A discussion document

ADR Reporting

We agree that patients/consumers need to be more directly involved in the pharmacovigilance system. We propose that Member States having implemented a patient reporting system share their experience and that lessons learnt be discussed at Community level. The option proposed by the Fraunhofer study to have the report validated by health care professionals seems appropriate.

PROPOSED SOLUTIONS ON PENDING ISSUES

AESGP has developed concrete proposals to better implement the legal provisions in three areas:

1. Literature search – frequency
2. Periodic Safety Update Report
3. Electronic submission of ICSR

We believe that our proposals take into account the profile of well-established substances while complying with the spirit of the legislation and ensuring protection of public health.

1. Literature search – frequency

The current legislation provides for a weekly search of the literature. For well-established substances, the safety profile is well-known and the impact of literature screening from the pharmacovigilance perspective is, in general, low. Based on our experience, a weekly search is not justified for such substances.

➔ Therefore, based on the recommendations of the CIOMS V[2], we suggest allowing a monthly search and reflecting this change in Volume 9a.

The current system of reporting cases published in the worldwide literature results in having the same report sent to the authorities multiple times. For well-established substances the situation is even worse as for some substances there may be more than 30 MAHs in one Member State required to submit the same literature reports to the Competent Authorities. This leads to a huge number of submissions with a considerable workload on both sides without major value added from a public health point of view.

➔ As a first step, we propose that sharing work and pooling resources between companies be facilitated. The second step would be for well-established substances to allow the submission of one master-report per substance. This could also be addressed in Volume 9a.

This proposal has been put into practice for 204 chemical substances and 199 herbals in Germany since 1 April 2003. One hundred and three companies are participating in this exercise. Scientific publications are reviewed on a monthly basis by competent employees and are assigned to one of four categories according to their importance in terms of pharmacovigilance purposes. The results of this screening are presented on a monthly basis in an internet-based system which enables customers

[2] "*Such searches should be conducted regularly with a frequency appropriate to the drug and any special situations, but in general not less frequently than once a month*" - Conclusions of the CIOMS V Working Group

to automatically retrieve and download scientific literature articles that are relevant for their pharmacovigilance purposes. Registered users have the opportunity of searching and viewing articles for distinct medicinal products, distinct time intervals and distinct categories or a combination thereof. They may order the full-text articles which form the basis of each included reference. If a particular reference has been given the status of a "potential case", users may order CIOMS I forms.

2. Periodic Safety Update Report

In application of Article 104(6) of Directive 2001/83/EC as amended, companies are required to submit all adverse reactions experienced with a given medicinal product via a Periodic Safety Update Report.

For medicinal products containing well-established substances, the main part of the PSUR is related to the active substance. This means that MAH with authorised medicinal products containing the same active ingredient will need to submit in their PSURs the same available information about this active ingredient. This results in many duplicates.

➔ **Our proposal would be to ease the process by installing a joint approach/work sharing for the bibliographic part of the PSUR**.

In addition, the submission has to be done according to a certain timeline. For medicines with well-established substances, this results in submitting similar files at different intervals, making the work of the Authorities difficult.

For this reason, we support the initiative currently on-going at Community level which has for purpose to **harmonise birthdates of substances** so that submission of PSURs for the same substance can be aligned. We would recommend that this initiative **be extended to all substances including herbals and products authorised in the EU before 1976**.

Harmonised birthdates would facilitate the work-sharing between companies marketing products with the same substance. The last step of the proposal would be **to allow the provision of the substance-related part of the PSUR only once on behalf of all companies manufacturing medicinal products containing that substance.**

This proposal is being piloted in Germany, and about 50 companies are participating in this joint-approach. Keydates/birthdates have been defined for 400 chemicals and 200 herbals.

As a consequence of the harmonisation of birthdates, the PSUR submission cycle has to be amended. Such a change should be possible via a **simple notification**, as recommended by the Heads of Medicines Agency[3], and not via a type II variation as is currently the case. To make this possible, we recommend modifying Volume 9a in this sense.

[3] The document titled 'Towards harmonised Birth Dates of MP in the EU', adopted by the Heads of Medicines Agencies on 17 October 2005 states that: "I*f both the MAH and competent authorities can agree a harmonised birthdate (which would require an amendment of the current PSUR submission schedule in some Member States) the change is a simple administrative change which has no implication for public health*".

3. Electronic submission of Individual Case Safety Reports (ICSRs)

The new legislation requires that adverse reaction be reported electronically save in exceptional circumstances. Those 'exceptional circumstances' are very restricted, namely, mechanical, programme, electronic or communication failures that prevent electronic reporting.

For SMEs dealing with well-established use medicines, the cost/benefit ratio is disproportionate. The rate of reporting is very low and of limited value for well-established substances. For example, in Germany, 18 MAHs provide 200 reports per year whereas 370 MAHs submit less than 10 reports. In addition, these SMEs usually have a simple computerised system in place not able to "host" E2B which requires a totally new and costly infrastructure.
Therefore, having an in-house E2B infrastructure is not reasonable for SMEs, both from a scientific point of view (low reporting, limited value for SMEs) and from an economic point of view (high cost, low frequency of use).

➔ Our proposal would be to facilitate the sharing of an E2B infrastructure between companies.

Again, this is a reality in Germany where our member association provides access to an electronic E2B-compatible database which can submit data automatically to the EMEA's E2B gateway as well as to portals of the national authorities. The service covers pre-marketing (clinical trial) and post-marketing requirements, including the establishment and evaluation of pharmacovigilance data such as suspected unexpected serious adverse reactions (SUSARs), adverse reactions, study reports, literature, etc., MedDRA coding and reporting requirements. The software includes a MedDRA browser and can establish E2B XML data, CIOMS I forms and CIOMS II Line listings.

Based on the German experience, we think that these proposals have demonstrated their usefulness and benefits. We urge the Commission to support such proposals and to consider including them in the revised version of Volume 9a. This would assist SMEs throughout Europe in complying with the legislation while focusing their resources on what is most critical from a pharmacovigilance and public health point of view.

Brussels, 12 May 2006