



Making Medicines Affordable

POSITION PAPER

EGA RESPONSE TO COMMISSION PUBLIC CONSULTATION:

AN ASSESSMENT OF THE COMMUNITY SYSTEM OF PHARMACOVIGILANCE

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EGA RESPONSE to Commission Public Consultation: An Assessment of the Community System of Pharmacovigilance

Type of stakeholder: Industry

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The EGA welcomes the opportunity to make recommendations to the current European Community system of Pharmacovigilance. The EGA recognises and supports the fact that all members of the pharmaceutical industry are responsible for the safety of their products in the interests of public health.

The EGA represents a group of companies which market generic medicinal products as well as similar biological (“biosimilar”) medicinal products. As biosimilar products are new on the EU market, this document will focus on the experience of the Community system of pharmacovigilance gained with medicinal products which have been on the market for a relatively long period of time and for which the safety profile is usually well-established. We will refer throughout this position paper to these products as *established products*.

To gain a marketing authorisation for generic medicinal products, applications cross-refer (after expiry of the data exclusivity periods) to safety information approved for the corresponding originator products. This cross-referencing makes good sense because the safety profile is usually well-established by then. Consequently the concept of established products, as referred to in this position paper, encompasses established products from the originator, generic and OTC industry.

It is well accepted that all industry sectors should follow the same pharmacovigilance rules, however once an active substance has a well-established safety profile, the pharmacovigilance requirements should be adapted to this situation. There is indeed a lot of room here to improve the current system to:

- rationalise and strengthen the system;
- make more efficient use of the resources available within industry and the Competent Authorities; and
- without jeopardizing - in fact, even improving - public health.

Adoption of many of the items mentioned below will reduce the amount of time spent on administrative tasks or other activities that do not really contribute to increased safety of the medicinal products. It should be noted that it is not the intention of the EGA to reduce the resources assigned to pharmacovigilance, but the objective is to use the available resources in an efficient way, focussing on the important mission of safeguarding the well-being of the patients who use our products by achieving the best possible risk-benefit ratio.

The recent report entitled ‘*An Assessment of the Community System of Pharmacovigilance*’, based on a study funded by the Commission, covers only Member States’ regulatory authorities and the European Medicines Agency. The EGA welcomes this consultation, involving all other important stakeholders in the European Community system of

Pharmacovigilance, such as industry, patients and healthcare professionals. We trust that the findings from this public consultation will provide the Commission with a complete picture of the functioning of the current system.

EGA comments on the specific areas highlighted in the Commission-sponsored study:

1. Data sources and safety issue detection

EudraVigilance (EV)

The EudraVigilance database is a database with great potential, once populated with Individual Case Safety Reports (ICSRs) and Suspected Unexpected Serious Adverse Reactions (SUSARs). It is possible to perform signal detection on all products on the EU market and authorities are able to extract specific cases from their country. The EGA strongly recommends the use of this EV database as the only source of safety information in the EU.

At this moment however it is not functioning in the optimum way:

- Some authorities are not ready to exchange data on ICSR electronically.
- EGA recommends that high priority should be accorded to achieving the full functioning of EudraVigilance as originally conceived, so that electronic reports may be received by EudraVigilance and then re-distributed to Member States and Marketing Authorisation Holders (MAHs) as required.
- Although the existence of Volume 9¹ suggests a harmonised approach in the EU, the reality is quite different. Several EU authorities prefer to have their own database. They require different cases (consumer cases, non-serious cases) than EudraVigilance which results in another source of information within the EU. Some require reports in local languages, which complicate the process as well as data consistency.
- Furthermore, it is apparent that when a company is deemed compliant with EudraVigilance, it by no means guarantees that the company complies with the requirements of all local databases. Some Member States have specific local requirements, which even at times contradict the requirements of EudraVigilance or require additional information to be sent with the reports. This deviation from the EV database/lack of harmonisation is counterproductive and does not help public health.
- To overcome the difficulty of assessing expectedness, the EGA recommends that industry provide all serious non-EU data to the EV database irrespective of expectedness. This is a deviation from Volume 9, but since a case could require expedited reporting in one Member State and no reporting in another it would be in the database ultimately, so it will give more complete information to the database and reduce bureaucracy. We welcome and appreciate that some EU authorities have already agreed to this principle.

¹ Volume 9 of the Rules Governing Medicinal Products in the European Union,
<http://europa.eu.int/comm/enterprise/pharmaceuticals/eudralex/index.htm>



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- The database will only be fully understandable when all information in the database is in English, so Member States & industry alike should be required to use the English language for EudraVigilance. Although we understand and recognise the sensitivity regarding the use of national languages, in the end our common goal is public health and it should be borne in mind that this could be put at risk when a case cannot be assessed or may be assessed differently because essential information is given in local language.
- Some Member States send reports they receive from healthcare professionals to all companies with a marketing authorisation in that country. These cases are included in the PSUR by the Marketing Authorisation Holders (MAHs). In the future it is proposed that all data from the PSUR be included in EudraVigilance. These cases will all be duplicate cases in EudraVigilance, because the company is not able to detect the duplicates. This other source of duplicate reports should be avoided as it requires resources to eliminate them and it has the potential to affect signal detection.
- One could even consider a more ambitious approach regarding reporting requirements. Currently industry sends ICSRs to the EMEA and to different Member States via the EMEA gateway. We suggest that industry reports ICSR only to EudraVigilance; the receiver address should be always the same i.e. “EudraVigilance”.

Other data sources

- All stakeholders must actively contribute to promoting a culture of notification of spontaneously reported adverse drug reactions (ADRs), since these are one of the key data sources for the conduct of pharmacovigilance activities.
- Patients (and caregivers), and healthcare professionals (HCP) are central to the provision of safety data to MAHs. The implementation of incentive measures in order to motivate notification of ADRs by HCP should be taken into account. The choice of methods should be made at the national level, as their success is partly dependent on the cultural environment.

Examples of these measures are:

1. Developing comprehensive programmes, with industry support or participation, in order to encourage reporting;
2. Establishing a feed-back system of information and dialogue with those reporters;
3. Linkage of the reporting to a service delivered to reporters; this service may take the form of a literature review on the same adverse drug reaction or on adverse reactions associated with the suspected drug;
4. The continuing evaluation of HCP should take into consideration the number and quality of report of ADRs per year, which should be conceded a credit value;
5. For job applications, continuous training in pharmacovigilance should be included in the *curriculum vitae*;

6. The promotion of a culture of notification should take into consideration HCP associations as well as patient/caregiver organisations.

- The educational programmes conceived to stimulate spontaneous reporting should be implemented at the general practitioner (GP) level as well as with physicians working in hospital setting. The promotion of spontaneous reporting of ADRs in the hospital setting opens up access to safety data related to unique groups of medicinal products or their combinations.
- Finally, it will be important to coordinate activities with academia as a sponsor of clinical trials and post-authorisation safety studies and as vehicle of education of HCP.
- Post-authorisation safety studies can supplement the routine data and played a decisive role in the update of safety data. However, regulations and legislation on post-authorisation safety studies are not harmonised throughout the EU.

Literature

Volume 9 requires each MAH to conduct a systematic literature review once weekly. It is largely recognised that this requirement triggers numerous literature reports, which is a waste of time and resources and which has the potential to affect signal detection. Since EudraVigilance has been operating, the issue of duplicate literature reporting has become even more evident. A sub-group of the EV Expert Working Group (EWG), representing all industry sectors is currently working on an EGA proposal regarding worldwide literature research. This proposal would contract out the literature search to a Contract Research Organisation (CRO). This organisation would be responsible for researching literature on behalf of the MAHs through a fixed protocol under defined contractual terms proposed by the EV EWG. The CRO would enter the data in E2B-compliant format into EudraVigilance on behalf of the MAHs.

This initiative will probably only be able to *reduce* the vast number of duplicates, not *eliminate* them, because companies cannot be forced to join the initiative. In addition there remains a problem of copyright, since pharmaceutical companies are commercial organisations.

A true solution to the problem of duplicate literature reports would be when the Member States combine the efforts and resources they currently spend on literature reports and set up a *literature agency* with the EMEA. This agency would conduct the literature searches and enter all reports into EudraVigilance, in an area which is open to all industry and Member States. Copies of articles would be available to the Members States. For the purpose of a PSUR the industry could buy a summary with line-listings from EudraVigilance and this could be used for the assessment of the active substance(s). This proposal would save time and money for Member States and also for industry as well as ensure that all literature is in the database, of good quality and available to all Member States.

Publication of an article in most scientific journals usually takes several months due to the detailed review processes required. Therefore case reports derived from literature are usually already over a year old. It therefore seems illogical to request a weekly literature



search from industry also because most journals are not even issued on a weekly basis but on a monthly basis. This is especially true for established medicinal products. It is also the responsibility of the author/healthcare professional to inform industry and/or the competent authorities of the case and when such a case requires action with regard to the safety of the product or active substance(s), we would certainly hope the industry/authorities had already been informed. Therefore we propose that a monthly search of the literature is adequate.

It could be envisaged that publication of adverse drug reactions (case reports) in the scientific literature should be according to a legal standard. Previous notification of the adverse drug reactions to the concerned competent authority and/or the MAH or if possible directly to 'EudraVigilance', inclusion of the commercial name of the suspected drug as well as the active principle in the literature report should be mandatory.

Signal detection

It is difficult for industry to retrieve a signal for established products. The company can try to address differences in reporting, absolute numbers of cases etc with the cases in their own database but this will rarely provide a complete picture because these products are likely to be marketed by several different companies in the EU. These are acting in countries having different cultures with regard to safety reporting. If there is an indication of a health issue, the company should ideally have access to the data of the other companies to get a clear view of the safety of a product. In fact, for products supplied by many manufacturers, the only signal a company can generate is that resulting from a change in their own product, maybe due to a change in the manufacturing process or the formulation.

A true signal for established products can only be found in the EudraVigilance database which contains all serious ADRs reported for a particular active substance from all MAHs in the EU market. One important case in a PSUR of company A can only be combined with other cases from other companies by the European authorities.

To conclude, signal detection for established products should be conducted using all available information, which can only be provided through EudraVigilance. It therefore falls to the Member States or the EMEA to combine all information in EudraVigilance and perform complete signal detection on established products.

Periodic Safety Update Reports (PSURs)

The Heads of Agencies (HoA) have agreed to an immediate move to a 3 year PSUR submission cycle from the grant of the authorisation of established products. In practice this will only work if all Member States adopt the same approach and give all MAHs certainty and transparency so that they can plan the writing of PSURs. When a generic product is authorised, the corresponding originator product operates usually under the 3-year PSUR submission cycle. Consequently the requirement regarding the PSUR submission cycle for established substances will be the same.

The EGA welcomes and supports the ongoing initiative of harmonised active substance birthdates. As a consequence all products containing the same active substance will have the same PSUR submission cycle, hopefully accepted by all regulatory authorities and companies.



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- The EGA supports a similar approach for older substances authorised before December 1976 (date at which Directive 75/318/EC came into force). Although they have been registered under a different legislation, for the purpose of pharmacovigilance and safety there is no reason to exclude them from the initiative. It will save time and effort for the authorities and industry if this initiative is also extended to older substances.
- We emphasise however that no local Type II Variations should be required for changing the PSUR cycle. This is important to give the initiative a real chance to take off.
- Transitional arrangements for the phasing in are also needed in order to avoid extra work in writing additional PSURs. For short periods of time there may be very few reports. The best way to submit those would be as a line-listing.
- The synchronisation of the submission of PSURs of products containing the same active substance will allow Member States to share the workload regarding the assessment of PSURs. It is expected that the assessment report, drafted by the Member State in charge of doing the assessment, is accepted by the other Member States. Established products may currently have different labelling across the countries, so ideally this assessment would result in harmonised safety information which is common across the EU, and provide useful and current information to patients, doctors, pharmacists, nurses and all other stakeholders.
- This PSUR assessment report should be made publicly available. The resulting ‘official’ safety profile of the active substance could be made available to local software vendors in a suitable form which can be implemented in the business software. This is the most effective way to make healthcare professionals familiar with the safety profile of an active substance.
- Physicians are able to refer to the “official” safety profile of an active substance.
- Patients will benefit from well-informed healthcare professionals.
- Nowadays varying information about the safety profile is included in these software packages of unclear origin. “Official” data should be an attractive source for software developers and soon a must for vendors.
- Regular updates are common in such business databases.
- The reporting frequency for at least unknown symptoms could be increased by providing easy accessible information.
- Having additional reporting tools for ADR reporting in such business software could help healthcare professionals to do the reporting.

2. The legal framework and new legal tools

As the study *Fraunhofer ISI 2005* states

“...the legal framework harmonises regulation, pharmacovigilance practice, product information, communication and action across the Member States”.

However in practice the implementation of the new legal framework and the new tools has not been done in a harmonised way. The complexity of the EU pharmacovigilance system may also have increased with EU enlargement. There may be some confusion regarding responsibilities.

The new legal framework has not at all addressed the issue of the increased duplications of effort and has not adequately adjusted the pharmacovigilance requirements to the lifecycle of the active substances. The new system also lacks appropriate involvement of other stakeholders like healthcare professionals and patients.

3. Decision-making in pharmacovigilance

From the EGA perspective, it is no longer acceptable that Article 30 procedures for established active substances are run by the CHMP and the Pharmacovigilance Working Party together with only the originator companies. The interested parties, as mentioned in Article 30, should encompass all industry sectors marketing the substance concerned. As generic and OTC companies have the same responsibility regarding pharmacovigilance they need to be included into the process.

4. Impact of communications and actions

- As the *Fraunhofer* report states, the “*coordination between agencies and MAHs should be improved...*”. We confirm that communication and coordination are not optimally effective.
- We expect each agency to make a real effort to characterise the MAHs that have medicinal products authorised in their territory in order to develop a consistent attitude to promote collaboration between stakeholders.
- Most companies are very open with regard to their ideas and approaches in pharmacovigilance. Unfortunately in some countries it is very difficult to get enough information on specific cases because a privacy law or other laws inhibit good contact with the treating physician or reporting healthcare professional. Furthermore due to lack of understanding of the role of industry, some reporters do not want to cooperate on giving additional information on the cases they reported.
- Healthcare professionals may report to the Member States and their reports are forwarded to industry. Unfortunately, however, the information in these cases is scanty and some Member States are unwilling to pursue any follow-up activities.
- Some Member States also do not forward or exchange data of the ICSRs with MAHs.
- A positive approach and attitude towards industry would greatly assist in this regard. Training of healthcare professionals in pharmacovigilance could contribute to solving the problem. The pharmaceutical industry could take part in this by educating healthcare professionals with whom they have contact.



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- Additionally, EGA supports EFPIA's suggestion that when a problem arises in the EU it should be possible to have one single contact, representing all Member States, with whom the MAH can discuss communication of safety information.
- We can conclude that only through effective collaboration and common understanding between pharmaceutical companies, regulators and other stakeholders, the highest level of safety for patients will be achieved.

5. Facilitation and monitoring of compliance with pharmacovigilance requirements

Audits (internal or external) and inspections of pharmaceuticals companies are a well-accepted mechanism to ensure that MAHs comply with pharmacovigilance regulatory obligations. It happens however that Standard Operations procedures that have changed according to the wishes of one inspector are then rejected by the next inspector. It would be very helpful and timesaving for all parties if there was agreement and harmonisation between the different pharmacovigilance inspectors nationally and internationally.

The Qualified Person (QP) responsible for pharmacovigilance is ultimately responsible for making sure that the pharmacovigilance systems are in place and that the legal pharmacovigilance requirements are met. However, all inspectors should accept that there must be some delegation.

According to the amended Directive 2001/83/EC, a detailed description of the pharmacovigilance system is to be included in the MA application. It should be acknowledged that this requirement represents a 'snap shot' in time as per other formal documents in an application like manufacturing licences etc. As changes of the pharmacovigilance system will happen very frequently, we suggest that the Summary of Pharmacovigilance System (SPS) is placed at a central location accessible to the regulatory authorities. In the MA application, a less detailed outline of the pharmacovigilance system would be submitted to comply with the new legal requirement and this would reference the SPS. It would be envisaged that this would be at most one or two pages, and would not go into the fine detail which would render it out-of-date within months of the application. Responsibility is placed on the EU QP for pharmacovigilance to ensure that the SPS is kept up-to-date. The SPS could contain all the information set out in Section 5 of the guideline on monitoring of compliance with pharmacovigilance regulatory obligations and pharmacovigilance inspection.

Last but not least, the EGA supports the conclusion of the *Fraunhofer* report that mentions that Member States should be exposed to process audits on a regular basis.

6. The need for quality management and continuous quality improvement.

Healthcare professionals may report cases to national authorities. These cases are forwarded to the industry. Sometimes these cases are poorly documented. Usually it is not possible to tell if any attempts have been made to gather follow-up information. Some Member States clearly state that they do not perform follow-ups on the request of industry. Bearing in mind that the company concerned has in-depth knowledge of the products, we propose that in specific cases it should be possible to request follow-up on a case reported to industry by the

authorities. This should be applied to cases on products with a risk management plan, or investigation of possible signals.

EGA comments on experiences of the Community system overall

The EGA firmly holds the opinion that pharmacovigilance is an important task of all the stakeholders mentioned. The establishment of the EudraVigilance database is a major step forward which, when functioning to its full potential, will be very valuable in supporting the efforts to protect public health with regard to the safety of drugs. In general, industry supports the legislation and published guidance and accepts responsibility to ensure adherence to these requirements. Most of the challenges industry is facing, are derived from different approaches in different countries.

EGA comments on any part of the Community system

With respect to EudraVigilance specifically we would like to state that the experience with the EMEA overall with regard to the implementation of the e-ICSR implementation and registration has been positive. The assistance at the EMEA for technical and administrative help has been very good.

It may be helpful if all Member States identify ‘risk’ products by perhaps extending the current UK ‘black’ triangle scheme to all EU countries. This would apply to medicinal products for which a risk management plan is required.

EGA comments on how our industry could better contribute to the Community pharmacovigilance system

As suggested above, when industry can save time in administrative procedures, resources can be re-allocated to the point of need, so enhancing the capacity to carry out meaningful pharmacovigilance activities serving public health.

EGA comments on suggestions to strengthen the Community pharmacovigilance system

Suggestions are given throughout the position paper.

Any other EGA comments

More and more pharmaceutical companies are becoming global, with a global pharmacovigilance system. The abolition of regional differences in pharmacovigilance requirements would be in the interests of the general public. The International Conference on Harmonisation (ICH) attempts to harmonise different views in different regions, and this approach deserves the full support of the European Union. We trust that global requirements and ongoing international discussions are kept in mind when considering implementation of any changes resulting from the current consultation process.