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Commission Public Consultation: An Assessment of the Community System of Pharmacovigilance

The Commission today launches a public consultation on the Community system of pharmacovigilance. The objective of the consultation is to collect the views of stakeholders on the community system, including comments on the current functioning of the system and how it might be further developed.

1. What is pharmacovigilance?

Pharmacovigilance is the process and science of monitoring the safety of medicines and taking action to reduce risks and increase benefits from medicines. It is a key public health function. Pharmacovigilance comprises:

- Collecting and managing data on the safety of medicines
- Looking at the data to detect ‘signals’ (any new or changing safety issue)
- Evaluating the data and making decisions with regard to safety issues
- Acting to protect public health (including regulatory action)
- Communicating with stakeholders
- Audit, both of the outcomes of action taken and of the key processes involved.

Those directly involved in pharmacovigilance include:

- Patients as the users of medicines
- Doctors, pharmacists, nurses and all other healthcare professionals working with medicines
- Regulatory authorities including the EMEA and those in the Member States responsible for monitoring the safety of medicines
- Pharmaceutical companies, and companies importing or distributing medicines

2. The Current EU system

The legal basis for pharmacovigilance in the EU¹ is given in Directive 2001/83/EC (as amended) and Regulation (EC) No 726/2004². In addition, detailed guidance is provided in Volume 9 of Eudralex (the Rules Governing Medicinal Products in the European Union)³. The current EU pharmacovigilance system is organised with functions, responsibilities and accountability shared between the Member State competent authorities, the European Medicines Agency (EMA) and European Commission. The EMA has responsibility for co-ordinating the pharmacovigilance activities of the Member States. The exact division of responsibilities changes depending of how a particular medicine is authorised. If a medicine has been authorised through the national authorisation mechanisms, most (but not all) of the functions, responsibilities and accountability for pharmacovigilance rest with the Member States. In contrast, for centrally authorised medicines, that is, those

¹ For this consultation whenever the terms ‘EU’ or ‘Community’ are used it should be noted that the current system applies to the 25 Member States of the EU plus the European Economic Area members Norway, Iceland and Lichtenstein.

² Directive 2001/83/EC (as amended) and Regulation (EC) No 726/2004 (see <http://pharmacos.eudra.org/F2/eudralex/vol-1/home.htm>)

³ For the latest draft proposals for Volume IX of Notice to Marketing Authorisation Holders see http://pharmacos.eudra.org/F2/pharmacos/docs/Doc2005/12-05/draft%20of%20Volume%20a_12_2005.pdf

authorised through the central Community authorisation procedure, more of the functions, responsibilities and accountability for pharmacovigilance fall to the EMEA and European Commission. See Annex 1 for more information.

3. Why we need an assessment of EU Pharmacovigilance

Pharmacovigilance is a key public health function and there is a need to strive to ensure it is optimally effective. The current system of pharmacovigilance in the EU is complex and there is potential for duplication of effort, as well as the potential for confusion of responsibilities. This is particularly true now with the introduction of innovative products, some utilising innovative technologies. Furthermore, with globalisation of the pharmaceutical market, products often enter different global markets simultaneously with exposure of large numbers of patients occurring in a short period of time.

Our society is changing and the expectations of EU citizens are also changing. There is a need to ensure that our pharmacovigilance systems are robust but also transparent and we need to consider the appropriate level of involvement in the system of different stakeholders, including healthcare professionals and patients.

Although evolving over time, our current system of pharmacovigilance in the EU has been established for a number of years and it is an appropriate time to assess our system and judge whether it should be further strengthened. An assessment of EU pharmacovigilance is particularly relevant at this time as the revised EU pharmaceutical legislation entered into force in late 2005 and 2004 brought ten new Member States into the system.

4. Information relevant to this consultation

To inform the consultation and stimulate the debate the Commission today publishes a report entitled “An Assessment of the Community System of Pharmacovigilance”. This study, funded by the Commission, was conducted by the Fraunhofer Institute Systems and Innovation Research in collaboration with the Coordination Centre for Clinical Studies at the University Hospital of Tuebingen. The study was based on collection of data through questionnaires and interviews of staff working in pharmacovigilance in Member State regulatory authorities and in the European Medicines Agency. The study was requested by the European Commission and started in January 2005 and the final report is now available. The core recommendations are reproduced at Annex 2 for ease of reference. Please note that the study report authors are independent of the Commission which does not necessarily endorse all of the report’s findings.

It should also be noted that many of the findings of the study are already being addressed. There is extensive ongoing work to strengthen the Community system which should be taken into account. This includes:

- the implementation work on the new legal tools introduced with the adoption of the revised pharmaceutical legislation, see Annex 4 and also:
 - <http://pharmacos.eudra.org/F2/pharmacos/new.htm> (of particular note are entries on 21 December 2005 and 14 March 2006)

- <http://www.emea.eu.int/hums/general/direct/legislation/legislationintro.htm>
- the work of the Heads of Medicines Agencies European Risk Management Strategy. Of particular note is the “Implementation of the Action Plan to Further Progress the European Risk Management Strategy: Rolling Two-Year Work Programme (Mid 2005 – Mid 2007)”. The key initiatives from this work plan are at Annex 3 and the full document is available at:
 - http://heads.medagencies.org/heads/docs/ERMS_actionplan_20051216.pdf
- inclusion of pharmacovigilance in the Commission proposal for the 7th Framework Programme, see especially pages 17 to 19 at:
 - (http://europa.eu.int/eur-lex/lex/LexUriServ/site/en/com/2005/com2005_0119en01.pdf)
- the proposal for a core pillar on pharmacovigilance in the innovative medicines initiative, available at:
 - (http://europa.eu.int/comm/research/fp6/index_en.cfm?p=1_innomed)

5. Have your say - the Commission seeks your views on the current system.

We want to know what you think about the European Community system of Pharmacovigilance. Make your voice heard and send your written comments, by 12 May 2006, to Peter Arlett at the European Commission.

Please feel free to:

- consider the specific areas highlighted in the Commission sponsored study (see Annex 2) which can be summarised as follows:
 1. Data sources and safety issue detection
 2. The legal framework and new legal tools
 3. Decision making in pharmacovigilance
 4. Impacts of communications and actions
 5. Facilitation and monitoring of compliance with pharmacovigilance requirements
 6. The need for quality management and continuous quality improvement.
- comment on your experiences of the Community system overall
- comment on any part of the Community system (see section 1 for a breakdown of the system)
- comment on how you could better contribute to the Community pharmacovigilance system
- make suggestions on how to strengthen the Community pharmacovigilance system.

Please use the template provided at Annex 5 and indicate clearly which category of stakeholder you belong to and, if relevant, what organisation you represent. Electronic submissions are preferred and should be sent to peter.arlett@cec.eu.int Please note that your consultation response will be made public.

Please note that the Commission will be holding two workshops in April or May 2006 as part of the public consultation. One will be for patient groups and healthcare professionals, the other for the pharmaceutical industry. In addition the Commission

will be holding discussions with regulators and the Member States. Specifically regarding the workshops, places will be limited and we cannot guarantee to accommodate everyone that would like to attend but if you would like an invitation please email your name, the organisation you represent and all relevant contact details to peter.arlett@cec.eu.int. As places are limited priority will be given to European organisations. All requests for the workshops should be sent by 31 March 2006.

This consultation is one key way that we can ensure that we strengthen pharmacovigilance, making it fit for the enlarged Community for decades to come and hence effectively protecting the health of citizens in the EU and beyond. Thank you for taking the time to read this document and thank you, in advance, for any contribution you make to this consultation.

*Remember, the deadline for comments is 12 May2006 - If you wish to clarify any aspect of this consultation then please email peter.arlett@cec.eu.int
Thank you for your help.*

**European Commission
15 March 2006**

ANNEX 1 – The Current Community System of Pharmacovigilance

The Current EU system: a (very) high level summary

The legal basis for pharmacovigilance in the EU is given in Directive 2001/83/EC (as amended) and Regulation (EC) No 726/2004⁴. In addition, detailed guidance is provided in Volume IX of Eudralex⁵. The current EU pharmacovigilance system is organised with functions, responsibilities and accountability shared between the Member State competent authorities, the European Medicines Evaluation Agency (EMA) and European Commission. The EMA has responsibility for co-ordinating the pharmacovigilance resources and work of the Member States. The exact division of responsibilities changes depending of how a particular medicine is authorised. For medicines authorised through the national authorisation mechanisms most (but not all) of the functions, responsibilities and accountability for pharmacovigilance are with the Member States. In contrast, for centrally authorised medicines, that is, those authorised through the central Community authorisation mechanism, more of the functions, responsibilities and accountability for pharmacovigilance are with the EMA and European Commission.

Data collection and management

Data sources for the conduct of pharmacovigilance include: spontaneously reported adverse drug reactions (ADRs), periodic safety update reports from pharmaceutical companies, data on the use of medicines, clinical trials and epidemiological studies. Patients and healthcare professionals are central to providing safety data. Industry has legal responsibilities in collecting, assessing and transmitting data. The Member States play a key role in the collection of data, from healthcare professionals, from academic institutions and from pharmaceutical companies. The EMA also collects data particularly from pharmaceutical companies and the Member States. Although Member States are responsible for many aspects of data management, a Community pharmacovigilance database, Eudravigilance, is operational and being further developed.

Safety ‘signal’ detection

Signal detection is the shared responsibility of pharmaceutical companies, national competent authorities and the EMA. The lead responsibility changes depending on the authorisation type. Healthcare professionals also have an important role in alerting the authorities or industry to suspected safety concerns. Patients should also raise their concerns with their healthcare professional.

Regulatory assessment and decision making

Between the authorities, responsibilities depend on authorisation type, with the Member States responsible for nationally authorised products (some but not all of the Member States having specific ‘safety of medicines’ committees) and the EMA (through its Committee for Medicinal Products for Human Use - CHMP) responsible for centrally authorised products. The EMA / CHMP also have responsibility for

⁴ Directive 2001/83/EC (as amended) and Regulation (EC) No 726/2004 (see <http://pharmacos.eudra.org/F2/eudralex/vol-1/home.htm>)

⁵ For the latest draft proposals for Volume IX of Notice to Marketing Authorisation Holders see http://pharmacos.eudra.org/F2/pharmacos/docs/Doc2005/12-05/draft%20of%20Volume%20a_12_2005.pdf)

nationally authorised products which are referred to them through one of the Community referral procedures. The industry also has an important role in assessing the safety of its products.

Regulatory Action to protect public health

Action might include adding warnings to product information, restricting the use of a medicine, or when the balance or benefits and risks is negative, removal of a product from the market. Once again, responsibilities depend on authorisation type. The Member States are responsible for all regulatory action relating to nationally authorised products and the EMEA and European Commission for action relating to centrally authorised products. When nationally authorised products are the subject of a Community referral, the CHMP gives its scientific Opinion which following consultation of the Member States, is converted into a European Commission Decision which is binding on Member States. The prescribing or dispensing behaviour of healthcare professionals, as well as medicines use by patients are the main targets of regulatory action taken.

Communication

Communication networks and responsibilities are complex, particularly with regard to the number of different stakeholders at different steps in the pharmacovigilance process. However, the main responsibility for communicating with healthcare professionals and patients about new risks or regulatory action taken falls to the Member States with the EMEA adopting an informal coordinating role, particularly for issues concerning a centrally authorised product or a referral to CHMP. The industry is also key in communicating on drug safety issues and healthcare professional and patient organisations can also fulfil a role in deciding on and distributing safety messages.

Audit

Audit in pharmacovigilance covers both process audit of the different process steps (data management, signal detection etc) and 'outcome audit' i.e. audit of the effect or public health impact of any regulatory action taken. Process audit, for all process steps, is not routinely conducted by all those involved in pharmacovigilance and outcome audit is only conducted in selected cases.

ANNEX 2 – Core recommendations from the study by the Fraunhofer Institute Systems and Innovation Research in collaboration with the Coordination Centre for Clinical Studies at the University Hospital of Tuebingen

Core recommendations

From the present research, we⁶ derive the following most important conclusions to make the European System of Pharmacovigilance more robust:

- The relative contribution of the different sources of safety information (Individual Case Safety Reports, Periodic Safety Update Reports, registries, consumption data, safety studies etc.) and respective resources for pharmacovigilance should be reviewed. The necessary statistical tools should be developed and specific requirements of small countries should be kept in mind.
- The new legislation strengthens the potential impact of tackling safety issues more pro-actively. This opportunity should be extensively used.
- The decision-making process should be reviewed; opportunities to streamline and fasten it should be identified.
- The impacts of communications and actions should be checked more systematically and from the lessons learned, the impact on prescription behaviour should be improved.
- The marketing authorisation holders are primarily responsible for the safety of their products. More resources are necessary to check if they comply with their legal obligations, and at the same time it should be identified how the requirements can be made as supportive as possible (e.g. as far as PSURs are concerned).
- General principles of quality management and continuous quality improvement should be introduced, among others:
 - (1) setting realistic and measurable targets for key interim impacts and for final outcomes;
 - (2) regularly checking if these target values have been reached;
 - (3) use of internal audit and peer review;
 - (4) identifying and deleting weaknesses (bottlenecks in procedures, under-performance or under-equipment of actors, waste of resources...).

⁶ Fraunhofer Institute Systems and Innovation Research in collaboration with the Coordination Centre for Clinical Studies at the University Hospital of Tuebingen

Annex 3 Key Initiatives that are included in the European Risk Management Strategy work program (Mid 2005 – Mid 2007)

Please note the full document is available at:

http://heads.medagencies.org/heads/docs/ERMS_actionplan_20051216.pdf

Risk detection

- Speeding-up the implementation of electronic reporting to EudraVigilance in accordance with ICH standards, at the level of both the National Competent Authorities and the pharmaceutical industry.
- Taking due account of experiences gained with such electronic reporting and addressing the needs for remedial actions through the newly established structure of the EudraVigilance Steering Committee and the EudraVigilance Expert Working Group.
- Further developing the EudraVigilance database by introducing additional functionalities, especially in the field of signal detection and data mining.
- Progressing the best evidence concept by developing a Concept Paper on best evidence based on the principles described in the 2003 ERMS.
- Identifying which areas require research with respect to the development of novel methodologies through participation in the Innovative Medicines Initiative.
- Publishing a list of medicines requiring intensive drug monitoring.
- Developing a network of academic centres to be involved in intensive drug monitoring.
- Exploring other methods of risk detection by taking due account of various initiatives undertaken by Regulatory Authorities.

Risk assessment

- Establishing the “new” Pharmacovigilance Working Party (PhVWP) with its revised mandate covering all medicinal products on the EU market, and reinforcing its scientific expertise taking into account the outcome of a gap-analysis.
- Optimising the interaction between the Committee for Human Medicinal Products (CHMP) and the PhVWP, and establishing the interaction between the PhVWP and the newly created Co-ordination Group for Mutual Recognition and Decentralised Procedures-Human (CMD(h)), building on the work already undertaken through the Best Practice Guide on the cooperation between the Mutual Recognition Facilitation Group (MRFG) and the PhVWP.
- Strengthening the existing peer review systems for the scientific work undertaken at the level of the CHMP and the PhVWP.
- Improving the methodology for benefit/risk analysis through the development of a Concept Paper which will be subject to public consultation.

Risk minimisation

- Fully implementing the new legal concept of risk management plans submitted by pharmaceutical companies as part of their marketing authorisation applications.

- Monitoring such implementation and taking any remedial action, where considered necessary.

Risk communication

- Initiating discussions with all involved parties on further increasing the transparency and streamlining the communication in the field of safety of medicines.
- Developing the component of an EU Transparency and Communication Strategy dealing with safety related information, including a Code of Conduct between the EU Regulatory Authorities and the pharmaceutical industry.

Other issues

- Fully implementing all other new legal tools to further strengthen the safety monitoring and to further increase transparency in the field of safety of medicines, monitoring such implementation and taking remedial action, where necessary.
- Applying a more proactive approach in the field of paediatric pharmacovigilance by developing a Guideline on paediatric pharmacovigilance and by establishing an inventory of all sources of data collection at EU level.
- Reinforcing pharmacovigilance in the area of vaccines by developing a Concept Paper on vaccine vigilance and by initiating discussions with the European Centre for Disease Prevention and Control (ECDC) on the development of methods and processes for the conduct of high-quality post-authorisation studies.
- Optimising the utilisation of scarce resources by fully implementing established work-sharing concepts (i.e. in the field of Periodic Safety Update Reports (PSURs)) and by identifying additional fields of work-sharing.
- Enhancing the overall quality of the EU Pharmacovigilance System by ensuring the availability at EU level of top quality scientific expertise through the establishment of an EU-wide up-to-date inventory of the available scientific expertise (including expertise from academia and learned societies), through the reinforcement of competence development and through adequate workload and resource planning at EU level.

ANNEX 4*Summary of the changes to the pharmacovigilance provisions in the pharmaceutical legislation*

The legal basis for pharmacovigilance in the EU is given in Directive 2001/83/EC (as amended most recently by Directive 2004/27/EC of 31 March 2004) and Regulation (EC) No 726/2004 of 31 March 2004. The updated legislation came into full force in the autumn of 2005. The key changes directly relevant to pharmacovigilance were:

- A description of the companies pharmacovigilance system and, where appropriate, risk management system is now part of the documentation that has to be submitted as part of the application for a marketing authorisation.
- Provision of pharmacovigilance data and information by the competent authorities to stakeholders (including patients) is a new requirement.
- The funding of the EMEA's pharmacovigilance functions must be public.
- The operation of the Community pharmacovigilance database (Eudravigilance) is given a clearer legal basis.
- The renewal of marketing authorisations will only normally occur once at five-years. This is combined with an increase in the frequency of provision by companies of 'Periodic Safety Update Reports' (PSURs): these will now be submitted 3-yearly rather than five-yearly.
- Companies must now notify the competent authorities before or at the same time as communicating pharmacovigilance 'concerns' to the general public.
- Variations to national marketing authorisations due to safety concerns may now form the basis of 'Community interest' referrals to the EMEA.
- The legal basis of pharmacovigilance inspections is now explicit.
- The competent authorities have the power to vary marketing authorisations without a variation application from a company.
- For centrally authorised products, the EMEA may request that the company arranges specific pharmacovigilance data to be collected from specific target groups.
- The penalties regulation will provide for Community action if companies are not compliant with the pharmacovigilance provisions of the legislation.

ANNEX 5 – template for responses (DEADLINE 12 May 2006 responses should be e-mailed to peter.arlett@cec.eu.int)

RESPONSE TO: Commission Public Consultation: As Assessment of the Community System of Pharmacovigilance

Your response will be put on the Commission's website.

Name⁷:

Type of stakeholder (e.g. patient/ healthcare professional/ regulator/ industry):

Organisation (e.g. European patient group or National industry association - if relevant):

Your comments:

- **on the specific areas highlighted in the Commission sponsored study which can be summarised as follows:**
 1. **Data sources and safety issue detection**
 2. **The legal framework and new legal tools**
 3. **Decision making in pharmacovigilance**
 4. **Impact of communications and actions**
 5. **Facilitation and monitoring of compliance with pharmacovigilance requirements**
 6. **The need for quality management and continuous quality improvement.**
- **on your experiences of the Community system overall**
- **on any part of the Community system (section 1 of this consultation paper describes the system and those involved directly)**
- **on how you could better contribute to the Community pharmacovigilance system**
- **on suggestions to strengthen the Community pharmacovigilance system.**
- **any other comments**

⁷ requests for attendance at the workshops should be sent separately to peter.arlett@cec.eu.int and should include the organisation you represent and your contact details. The deadline for these requests is 31 March 2006.