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 EU[1] is given in Directive 2001/83/EC (as amended) and Regulation (EC) No 726/2004[2]. 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 (EMEA) and European Commission. The EMEA 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

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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/htms/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
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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
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ANNEX 1 – The Current Community System of Pharmacovigilance

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

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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 EMEA 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 EMEA. 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 EMEA (through its Committee for Medicinal Products for Human Use - CHMP) responsible for centrally authorised products. The EMEA / CHMP also have responsibility for

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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, we[6] 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…).

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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 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.

Name[7]:

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
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- **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.

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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.

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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, we[6] 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 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.

Name[7]:

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.

Fraunhofer Institute
Systems and
Innovation Research

Assessment of the European Community System of Pharmacovigilance

Final Report – Final version

25 January 2006

European Commission
Enterprise and Industry Directorate-General, Unit F2, Pharmaceuticals

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Submitted by the

Fraunhofer Institute for Systems and Innovation Research, Karlsruhe, Germany

in collaboration with the

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Executive summary

Overview and aim of the study

Pharmacovigilance (PhV) is a key public health function. It is defined as the processes and science of monitoring the safety of medicines and taking action to reduce risk and increase benefit. It includes six phases:

1. Data collection
2. Data management
3. Signal detection
4. Safety issue assessment
5. Decision-making
6. Communication and action

The general aim of the present project was to analyse how the European central and EU Member States' medicines agencies collaborate with each other, the marketing authorisation holders (MAHs) and other stakeholders, in surveilling the adverse effects of pharmaceutical products, and to put forward recommendations to make the system more robust.

The work was based on a systemic perception of pharmacovigilance and combined the analysis of different aspects of the system: processes, stakeholders, resource availability and functional capability, gaps, strengths and weaknesses, as well as best practice. It was carried out by the Fraunhofer Institute for Systems and Innovation Research, Karlsruhe, Germany, and the Coordination Centre for Clinical Studies at the University Hospital of Tübingen, Germany, together with Prof. H.G.M. Leufkens from the Utrecht Institute for Pharmaceutical Sciences, University of Utrecht, the Netherlands, and Prof. U.M. Gassner, Department of Public Law and Research Centre for Law of Medicinal Products at the University of Augsburg, Germany.

The national medicines agencies, as well as the European Medicines Agency as the competent authorities were included in the research in several ways: interviews and a written survey were carried out with representatives, mainly the heads, of the agencies' pharmacovigilance units. Moreover, the Heads of Medicines Agencies Working Group for the European Risk Management Strategy and other experts were systematically involved in the design of the study and the discussion of preliminary findings and conclusions. The final results and recommendations, however, are the sole responsibility of the project team.

The main results of the study for general aspects as well as for the phases of pharmacovigilance are briefly reviewed in the following paragraphs, and the core recommendations are presented.

General aspects

The **legal framework** harmonises regulation, pharmacovigilance practice, product information, communication and action across the Member States. International co-ordination lends more power to regular action, this is especially true for the system for Centrally Authorised Medicinal Products (CAPs).

However, the legal system is also complicated because of the many responsible authorities involved; different procedures and responsibilities for products under the centralised and the non-centralised authorisation procedure. The system is very difficult to oversee despite the existence of detailed guidances.

Different implementation of the framework is caused by e.g. diverging health systems in the MS and different opinions which tasks should fall under the responsibility of the national authorities. The new Member States are not yet totally integrated and existing instruments are not fully applied.

At the moment, the emphasis strongly lies on the collection and analysis of spontaneous reports. This will remain important despite the fact that the recent safety crises have shown that other information and especially independent safety studies may be even more important to identify safety issues. The new regulatory system in place from November 2005 on will allow Pharmacovigilance Planning including a more proactive approach to pharmacovigilance by agencies and MAHs, and should be rigorously applied.

The analyses have shown that **staff numbers and technical resources** vary tremendously across agencies.

Table 0.1. Total national staff for PhV per capita

	PhV staff NCA[1] **[FTE per million capita]**	**PhV staff NCA+RC**[2] **[FTE per million capita]**
Minimum	0.2	0.2
Median	0.772	1.183
Maximum	4.6	4.6

Staff for pharmacovigilance, scientific and administrative.

Source: Fraunhofer ISI 2005

In some agencies the number of staff seems to be less than the minimum required to complete the necessary tasks. Sufficient resources are needed in the MS to reach comparable staff numbers relative to their population sizes. The median of agencies might be used as a minimum value for all agencies. The completion of all urgent tasks at every point in time must be guaranteed.

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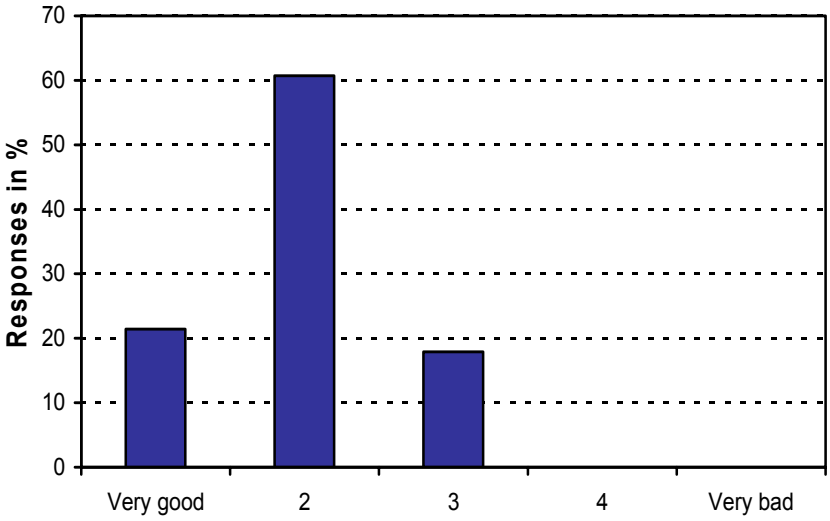
[1] National Competent Authority

[2] Regional Centre for Pharmacovigilance

The system draws strongly on the combination of **expertise**: expertise, assessments of safety issues and other documents developed at EU level can be used by the other agencies. However, the capability to assess safety issues does not exist in all agencies. As a result of the complex system and lack of experienced staff, some of the agencies need more support to be able to comply with the requirements. In some countries, it is difficult to find the necessary external experts especially for the assessment of safety issues, which also hampers their full contribution to the system.

With respect to the **collaboration between agencies**, the European system offers good and in general well-functioning structures, including the central role of the European Medicines Agency (EMEA).

Figure 0.1. Cooperation between national agencies and EMEA



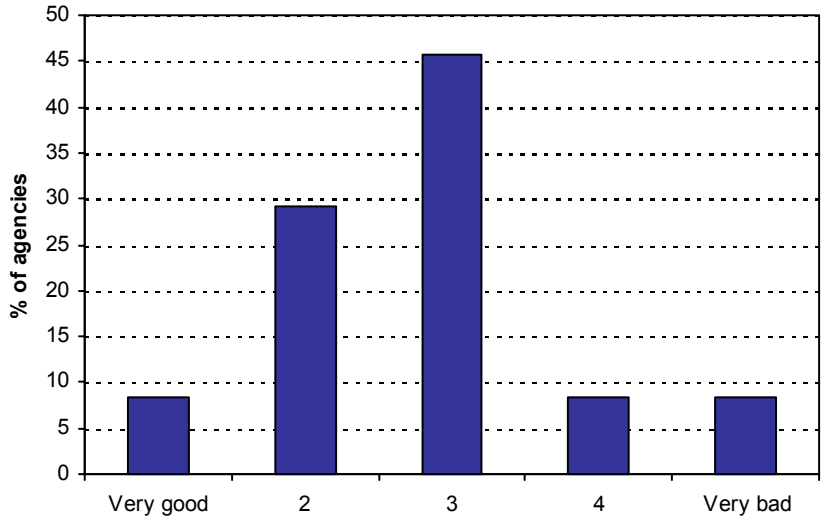
Source: Fraunhofer ISI 2005

On the other hand, being dependent on other agencies' work is sometimes a problem as long as the agencies' work is of different quality. Opinions differ as to what amount of work should be done at the national level, leading to different assessments of necessary and unnecessary duplication of work, which some of the agencies consider to be relatively high. Communication between MS agencies and EMEA is sometimes considered problematical.

The **collaboration with health-care professionals**, especially the physicians who directly impact on the prevalence of adverse drug reactions through their prescription behaviour, could be improved. Regional centres for pharmacovigilance are a promising approach to effectively communicate with health-care professionals.

The **compliance of Marketing Authorisation Holders** with the safety regulations for their products should be checked more rigorously.

Figure 0.2. Compliance of MAHs in analysis of signals



Source: Fraunhofer ISI 2005

Systematic **quality management** is not implemented in most PhV departments. The regulatory system does not provide clear goals or provisions in this respect. If implemented, nearly all agencies state that their audit procedures do not adequately ensure the quality of their work. In particular, only few agencies follow up the impact of communications on a routine basis. The continuous management and improvement of the agencies' quality of work is a major area for future action.

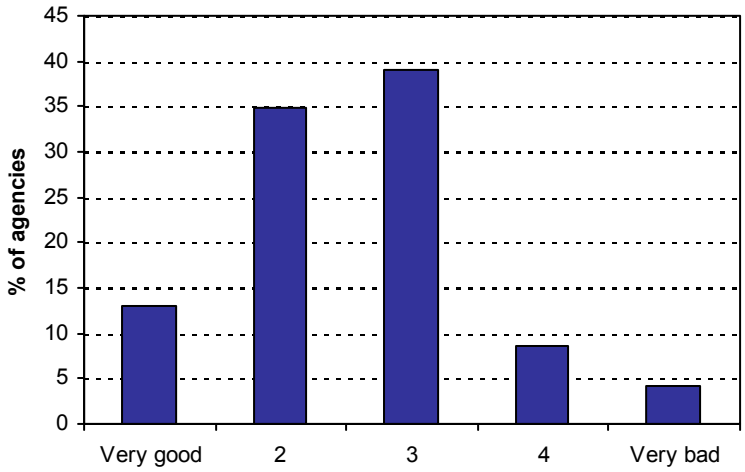
Data collection

The European system combines the Individual Case Safety Reports from a large population in order to increase the statistical power with which signals can be detected; small countries[3] with few reports in particular benefit from this.

The **agencies are not very well prepared for crises by routine data** (spontaneous reports coming from health-care professionals or marketing authorisation holders and Periodic Safety Update Reports (PSURs) from the marketing authorisation holders), their usefulness is restricted.

[3] The terms "small" or "large" for countries refer to the size of their population.

Figure 0.3. Preparation for last crisis by routine data



Source: Fraunhofer ISI 2005

Besides these "routine data", data especially on drug consumption, but also registries and other **data combining drug exposure and outcomes, including adverse drug reactions, are highly relevant**. Such registries exist in most of the countries. However, most agencies only have access to these data in exceptional cases, and they are quite infrequently used. This situation has to be improved.

Table 0.2. Existence and use of data on the consumption of medicines

	Exist	Use		
	N of agencies	**% never**	**% in except. cases**	**% routinely**
Sales data	24	0%	33.3%	66.7%
Prescription non-hospital	19	25.0%	40.0%	35.0%
Prescription hospital	14	47.1%	23.5%	29.4%

Source: Fraunhofer ISI 2005

Safety studies and other data that can supplement the routine data played a decisive role in the last safety crises. However, only very few prospective safety studies were prepared in the last years, and some of them were not performed independently of the producer of the drug studied. The funding of necessary studies is often not guaranteed. This open question is tackled by the new regulatory system which allows more pro-active data collection; its implementation is urgently required.

Research into the **safety of drugs for children** is disparately lacking, as is a database on products already on the market.

Data management

The system allows for a systematic sharing of work between the involved stakeholders (MAHs vs. agencies, as well as among different agencies). The **databases that are used in the national agencies** to manage case safety reports and other safety data vary greatly and are not all sufficiently specific to handle the necessary data.

Some **duplication of work** related to the handling of the same data exists at different agencies, especially at the EMEA, on the one side, and national agencies on the other. However, the issue of duplication of work (what is necessary, what is unnecessary duplication?) is assessed heterogeneously by the agencies. The coordination with other international partners could be improved.

Signal detection

EudraVigilance and the related procedures form the basis for the effective systematic pooling of and signal detection from spontaneous reports. The success of the combination of expertise and resources for signal detection depends on the **full implementation of the provisions**; with regard to the dependence on national resources and priorities, which at the moment cannot be taken as guaranteed and therefore needs continued supervision and support. This also holds true for the **statistical tools for signal detection**, as the tools for small numbers of cases in particular are still insufficient; improved techniques will have to be developed. As for data management, it does not seem that the best use is being made of work that is performed by the European system and by other international partners, respectively.

As hardly any controls are in place, it remains unclear whether the Marketing Authorisation Holders fulfil their role of first-line signal detection.

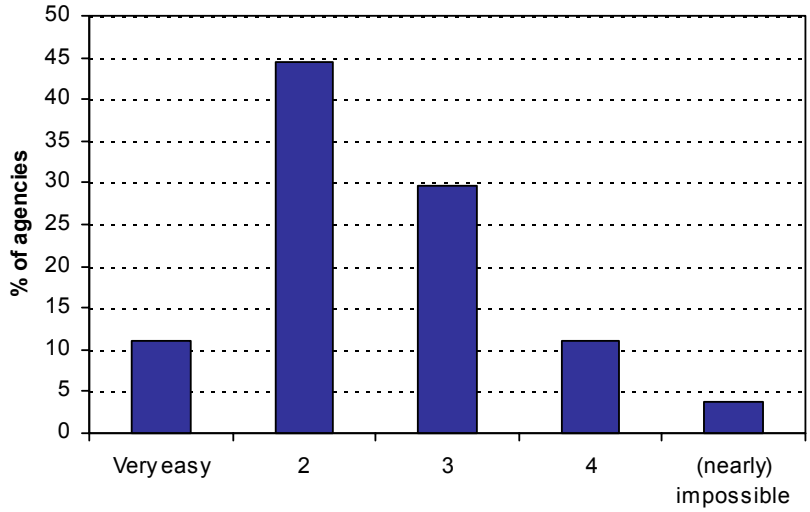
Safety issue assessment

The system allows sharing work and using assessment reports from other countries; generally, it comes to comparably good or better conclusions that other international systems.

The **share of work** and best use of international collaboration depends to a great extent on the quality of the work that the single agencies can contribute. Some agencies, however, admit that they do not yet have the ability to manage safety issues adequately on their own.

External expertise has not always been adequately used, partially because of difficulties in accessing external experts that some agencies experience.

Figure 0.4. Receive support from experts routinely

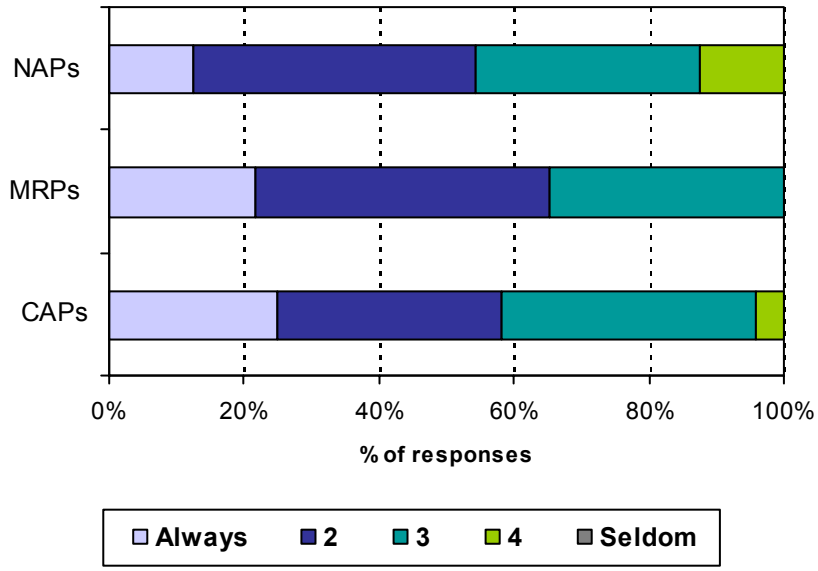


Source: Fraunhofer ISI 2005

Decision-making

Decision-making often takes too long, which is partially attributed to complicated structures within the CHMP and between CHMP and the Commission, especially in the case of referrals.

Figure 0.5. Decisions for safety issues found in adequate time



NAP: Nationally authorised product, MRP: Product authorised under Mutual Recognition Procedure; CAP: Centrally authorised product

Source: Fraunhofer ISI 2005

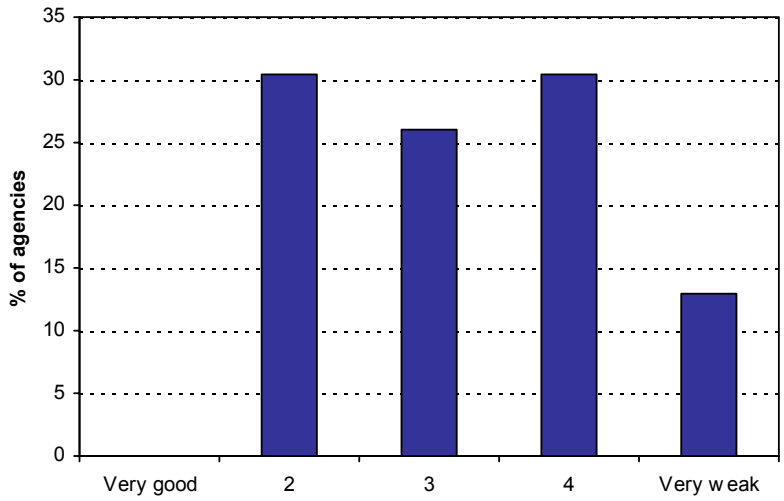
Communication and action

The system provides the structures to develop ?? timely and harmonised communications and actions, especially in those cases where satisfactory agreement has been obtained between the agencies and where sufficient time is available. However, the **time between the detection of a signal and action** was too long in some cases.

Regulatory transparency is very important to allow for consistent communication and argumentation of decisions. It is important to **adequately represent the Member States' particular situation** (e.g. regarding consumption patterns and epidemiology) in CHMP opinions or Commission decisions.

The **outcomes of regulatory action are only assessed in exceptional cases**. There is very little information about the reaction of prescribers to label information and label changes. Moreover, when information is available, the results are not very encouraging.

Figure 0.6. Influence of agencies' communications on prescription behaviour



Source: Fraunhofer ISI 2005

More should be done to ensure and supervise that communications and regulatory action result in the intended effects, especially by doing more research into the impacts of safety communication and action on prescription behaviour, but also by more inspections of MAHs with a pharmacovigilance focus.

Core recommendations

From the present research, we 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 (ICSRs, PSURs, 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…).

Abbreviations

ADE	Adverse Drug Experience
ADR	Adverse Drug Reaction
AE	Adverse Event
AERS	Adverse Event Reporting System
CADRIS	Canadian Adverse Drug Reaction Information System
CAP	Centrally Authorised Medicinal Product
CFR	Code of Federal Regulations (USA)
CHMP	Committee for Medicinal Products for Human Use
CIOMS	Council for International Organizations of Medical Sciences
EEA	European Economic Area
EMEA	European Medicines Agency
ERMS	European Risk Management Strategy
EU	European Union
FDA	Food and Drug Administration (USA)
GPMSP	Good Post-Marketing Surveillance Practice
HCP	Healthcare Professional
HMA	Heads of Medicines Agencies
ICH	International Conference on Harmonisation of Technical Requirements
ICSR	Individual Case Safety Reports
MAH	Marketing Authorisation Holder
MedDRA	Medical Dictionary for Regulatory Affairs
MHLW	Ministry of Health, Labour and Welfare (Japan)
MHPD	Marketed Health Product Directorate (Canada)
MRP	Mutual Recognition Procedure; Mutual Recognition authorised Product
MS	EU Member State
NAP	Nationally Authorised Medicinal Product
NCA	National Competent Authority
NDA	New Drug Application
NUIS	Non Urgent Information System
PAL	Pharmaceutical Affairs Law (Japan)
PASS	Post-authorisation Safety Study
PhVWP	Pharmacovigilance Working Party
PMDA	Pharmaceutical and Medical Device Agency (Japan)
PMS	Post-Marketing Surveillance
PSUR	Periodic Safety Update Report
RAS	Rapid Alert System
RC	Regional centre for pharmacovigilance
SPC	Summary of Product Characteristics
VAERS	Vaccine Adverse Event Reporting System (USA)
WHO	World Health Organisation

Abbreviation of country names

AT	Austria
BE	Belgium
CY	Cyprus
CZ	Czech Republic
DE-BFARM	Germany
DE-PEI	Germany-PEI
DK	Denmark
EE	Estonia
EEA-28	EMEA as responsible for 28 EEA countries
EI	Ireland
ES	Spain
EU-25	EU-25
FI	Finland
FR	France
GR	Greece
HU	Hungary
IC	Iceland
IT	Italy
LI	Liechtenstein
LT	Lithuania
LU	Luxembourg
LV	Latvia
MT	Malta
NL	Netherlands
NO	Norway
PL	Poland
PT	Portugal
SE	Sweden
SL	Slovenia
SV	Slovakia
UK	United Kingdom

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1 Overview

The present report summarises the project "Assessment of the European Community System of Pharmacovigilance" from December 2004 to September 2005. The general aim of the project is to analyse the way in which the European central and Member States' medicines agencies collaborate in the surveillance of adverse effects of pharmaceutical products among each other as well as with the marketing authorisation holders and other stakeholders, and to make recommendations to make the system more robust.

The work was based on a systemic perception of pharmacovigilance and combined the analysis of different aspects of the system: processes, stakeholders, resource availability and functional capability, gaps, strengths and weaknesses, as well as best practice.

The project comprised the following 7 tasks.

Phase I:

Task 1: System analysis and description of status quo

Task 2: Definition of goals in respect of effectiveness and efficiency

Task 3: Identification of critical success factors

Phase II:

Task 4: Identification and definition of performance indicators

Task 5: Gap analysis to identify strengths and weaknesses

Phase III:

Task 6: Identification of best practice

Task 7: Recommendations

The service contract was signed on 08 December 2004, and based on an amendment from 13 April 2005; its duration was not more than 10 ½ months. An extension of the duration by 60 days became necessary for organisational reasons and was granted by the European Commission. Accordingly, the interim report was due at 03 June 2005, the draft final report was due at 15 September 2005, and the final report at 11 November 2005.

2 Methods

2.1 Organisation and implementation of the project

2.1.1 Partners and subcontractors

The project was carried out by the Fraunhofer Institute for Systems and Innovation Research, Karlsruhe, Germany (Fraunhofer ISI, project leader) and the Coordination Centre for Clinical Studies at the University Hospital of Tübingen (KKS).

As subcontractors acted the Utrecht Institute for Pharmaceutical Sciences (UIPS), Prof. Dr. H.G.M. Leufkens, head of the Department of Pharmacoepidemiology and Pharmacotherapy, particularly to collaborate with the partner KKS in the preparation of the case studies and to give general advice, as well as Prof. Dr. U.M. Gassner, Full Professor of Public Law at the University of Augsburg and director of the research centre for law of medicinal products, to support the overview of the legal framework.

2.1.2 Advisors

Instead of a formal steering committee for the project as suggested in the tender, it was agreed with the Commission to ask the Members of the Heads of Medicines Agencies ERMS Working Group to act as advisors. Additional experts from academia and industry as well as the subcontractor Prof. Leufkens joined this group. The advisors were primarily asked to participate in an interim meeting to discuss preliminary results and to support the development of critical success factors and performance indicators in two Delphi surveys.

2.1.3 Agreements of confidentiality

To ensure that potentially sensitive data were kept confidential by all concerned persons, and to allow the project to use confidential data from the agencies, agreements of confidentiality were signed both between the agencies and the project group as well as between the advisors and the project group.

2.1.4 Time schedule

The service contract was signed on 08 December 2004, and the work started directly after that. The organisation of the interviews proved to be much more time-consuming than expected for several organisational reasons. Besides this, the envisaged data of the HMA ERMS survey were not available until the beginning of June 2005.

The delay was not considered as an irreparable problem as some tasks (including the Delphi survey on indicators and critical success factors) could be shifted after the expert workshop without hampering the quality of the project's outcomes. None of the tasks described in the tender were neglected or dropped.

To have the questionnaire survey quite late in the course of the project offered the chance to include into the questionnaire survey the finalised set of the performance indicators instead of a draft set as it was planned. The earlier plan would have re-

quired asking the agencies for data more than once and thus the workload for the agencies could be reduced. Additionally, the questionnaire's quality was improved as an instrument for a potential future routine monitoring of the European pharmacovigilance system.

To ensure the quality of the project's results it was important that the remaining tasks could be performed with the time budgets planned originally. Therefore, the Commission was asked for and accepted an extension of the duration of the contract by four weeks and a slightly reduced time for the review of the final report. Based on an amendment from 13 April 2005; its duration is not more than 10 ½ months. A second extension of the duration by 60 days was granted by the European Commission. Accordingly, the interim report was due at 03 June 2005; the draft final report was submitted at 15 September 2005.

2.2 Tasks and methods

The work was divided in seven tasks (Table 2.1).

2.2.1 Task 1: System analysis and description of status quo

Task 1 was the first step in project Phase I (Description of the current system based on submitted documentation, questionnaires and site visits). It consisted of two subtasks. Based on an extensive analysis of scientific literature, previous reports, and previous studies, as well as on official documents from internet and national competent authorities, the specific features of the European Community system of pharmacovigilance that are relevant for its functioning were defined. One main output of this exercise is a review of the regulatory situation in the EU, which can be found in paragraph 3.1. The other output is the description of the processes in pharmacovigilance carried out by the national agencies and the EMEA based on the empirical data-collection with interviews and written survey.

Table 2.1. Tasks and work steps

Task/Milestone/Deliverable		Detailed work steps
D1[4]	*Detailed work plan*	
MS1	*Kick-off meeting with Commission*	
Task1	**System analysis**	Analysis of scientific literature
		Analysis of documents
		Written survey of agencies
		Personal interviews with agencies
		Telephone interviews with stakeholders
MS2	*Description of the relevant features of the system*	Working paper on regulation
Task2	**Goals**	See Task 1
MS3	*List of effectiveness/efficiency goals*	Analysis of literature, Delphi process
Task3	**Critical success factors**	Analysis of the literature
		Personal interviews
		Delphi process
MS4	*List of critical success factors*	–
Task4	**Performance indicators**	Analysis of the literature
		Personal interviews
		Delphi process
		Case studies
MS5	*List of validated and practicable performance indicators*	–
Task5	**Gap analysis**	Comparison of indicators with success factors
		Interviews
MS6	*List of differentiated strengths and weaknesses*	–

[4] MS: Milestone; D: Deliverable

Task/Milestone/Deliverable		Detailed work steps
D2/MS7	*Interim report and interim meeting*	–
Task6	**Best practice**	Comparison of indicators with success factors
		Interviews
MS8	*List of best practice approaches*	–
Task7	**Recommendations**	Expert workshop
		Optimisation tree
MS9	*Expert workshop finished/ list of recommendations*	–
D3/MS10	*Draft final report and final meeting*	–
D4/MS11	*Final report*	–

Task 1 was completed by telephone interviews with additional stakeholders from industry, science and independent organisations on specific topics.

2.2.2 Task 2: Definition of goals in respect of effectiveness and efficiency

Task 2 used the same methodological approaches as for task 1 (analysis of scientific literature, reports, studies, interviews with representatives of the competent authorities, representatives of the industry). On this basis, the goals in respect of effectiveness and efficiency of the European Community system of pharmacovigilance were defined.

Initially it was intended to supplement a provisional list of goals that was based on the literature by the respective results from the personal interviews, and to ask the advisors in a Delphi-process to comment on the list. However, the interviews revealed nearly no new aspects in this respect; most of the interviewees found the actual scope of pharmacovigilance (with some modifications) in general sufficient, many referred to the related WHO definition. Therefore, there was no need to elaborate more on the aspect of additional goals for pharmacovigilance in the Delphi process.

2.2.3 Task 3: Identification of critical success factors

Critical success factors are those elements of the whole process that determine its performance and can be modified to improve a system. For the 25 EU Member States and EMEA the most critical success factors for an effective and efficient functioning of the pharmacovigilance system (with respect to cost-effectiveness, time-efficiency, quality and safety) were identified firstly on the basis of a systems approach supported by data from the interviews and literature. First results were presented in Brussels at the expert workshop on 15 June 2005. After this, the advi-

sors were asked in a Delphi-process to comment on the list of critical success factors.

2.2.4 Task 4: Definition of performance indicators

Task 4 was the first task in project Phase II (Assessment of the robustness of the current system highlighting both strengths and weaknesses).

Within task 4 a set of performance indicators was developed based on literature and interviews. The indicators were distinguished in input, process, and output indicators. The advisors were asked to support the evaluation of the indicators in the Delphi-process. This task was delayed because of the late completion of the interviews which formed an important input also for this step.

2.2.5 Task 5: Gap analysis to identify strengths and weaknesses

Task 5 identified strengths and weaknesses of the pharmacovigilance system on basis of performance indicators, critical success factors and effectiveness/efficiency goals.

Most important working step was the analysis of the interview and agency survey data. They were partially combined with the data from the two ERMS surveys, which assessed the old MS in 2002 and the new MS in 2004 (more details are found in chapter 2.3).

2.2.6 Task 6: Identification of best practice

This was the first task of Phase III (Proposals to make the European Community system of pharmacovigilance more robust).

Many interesting approaches to solve at least some of the issues that are discussed within the system were collected from the literature and even more from the interviews with the national agencies. On the national level, some of the problems have been resolved by measures which could partially serve as models for the whole EU system.

2.2.7 Task 7: Recommendations

According to the original project plan, recommendations for making the European Community system of pharmacovigilance more robust should be deducted based on task 6 and discussed in the expert workshop. Since the expert workshop could not be postponed for organisational reasons, draft recommendations were derived basically from the literature review and the interviews and discussed at the expert workshop. The draft character of the recommendations was in accordance with the requirement that the final recommendations were as far as possible independent from the influence of the stakeholders (e.g. advisors), but nevertheless were informed by external expertise.

The preliminary conclusions and recommendations were discussed with the advisors during the workshop on June 15.

2.3 Collection and analysis of data

The empirical approach was based on personal interviews with representatives of the competent authorities and a written agency survey. In addition, two Delphi-surveys were carried out.

Own data were as far as possible collected with the same questions that were used in the earlier surveys of the Heads of Medicines Agencies ERMS Working group, but nevertheless are not totally comparable with the ERMS data. In addition, the samples differ in the countries that are covered. The ERMS-survey of 2002 covered the 15 old EU Member States with 2 datasets for Germany (BfArM and PEI) as well as NO (n=17 datasets), the 2004 ERMS-survey comprised the 10 New EU Member States.

Table 2.2. Datasets for the analyses

	N of data-sets
ERMS survey 2002 (Old EU MS, 2 datasets from DE, plus NO)	17
ERMS survey 2004 (New EU MS)	10
Own survey:	
Interviews (25 EU MS, one additional dataset from second German agency, plus EMEA)	27
Written survey completed by agency (25 EU MS, one additional dataset from second German agency, plus EMEA, plus 3 EEA MS: IC, LI, NO)	30
One common dataset for the 2 German agencies, plus one for the EU-25	2
Own survey maximum number of datasets	32

Source: Fraunhofer ISI 2005

Caused by the different samples used, quite frequently different numbers of respondents have to be taken into consideration; missing values for single countries add to this and lead to variable sample sizes, but only to small differences in the appearance of some figures (single countries missing etc.).

2.3.1 Interviews

27 site visits in all 25 EU Member States and at the EMEA have been conducted (Table 2.3).

Table 2.3. Site visits for interviews

Date of site visit	Country[5]	City	carried out by
10.06.2005	Latvia	Riga	ISI
09.06.2005	Estonia	Tartu	ISI
09.06.2005	Lithuania	Vilnius	ISI
07.06.2005	Ireland	Dublin	ISI
02.06.2005	Poland	Warszawa	ISI
30.05.2005	Czech Republic	Praha	ISI
26.05.2005	Greece	Athens	ISI
24.05.2005	Cyprus	Lefkosia	ISI
20.05.2005	Hungary	Budapest	ISI
19.05.2005	Slovak Republic	Bratislava	ISI
18.05.2005	Malta	Gzira	KKS
11.05.2005	Italy	Roma	KKS
10.05.2005	Portugal	Lisboa	ISI
09.05.2005	Spain	Majadahonda - Madrid	ISI
04.05.2005	Sweden	Uppsala	KKS
03.05.2005	Finland	Helsinki	KKS
02.05.2005	Denmark	Copenhagen	KKS
02.05.2005	France	Saint-Denis	ISI
27.04.2005	Germany-PEI	Langen	KKS
26.04.2005	Germany-BfArM	Bonn	ISI and KKS
20.04.2005	UK-MHRA	London	ISI
14.04.2005	Belgium	Brussels	KKS
12.04.2005	Austria	Wien	KKS
07.04.2005	Luxembourg	Luxembourg	KKS
07.04.2005	Netherlands	Den Haag	KKS
04.04.2005	Slovenia	Ljubljana	KKS
16.03.2005	EMEA	London	ISI and KKS

The site visits were carried out by only four persons (two senior researchers from both contractors each) to ensure sufficient consistency in the carrying-out of the interviews.

The interviews were done on the basis of an interview guide and took about four hours each. In most cases, the agency's head of pharmacovigilance and one or two members of the staff, sometimes also the head of the division were present at least for a part of the time. The main topics of the interview guide are questions with respect to process activities (especially data collection, data management, quality control/quality assurance, safety signal detection, safety issue assessment, decision making process, action plans to protect public health, communication process with stakeholders, quality assurance), the relevant stakeholders and questions with respect to the resource availabilities/functional capabilities of these stakeholders.

The collected interview data were stored in an MS-Access database to allow easy handling and the production of overviews on the answers to specific questions

[5] In Germany two agencies are responsible for PhV on the national level, the Paul-Ehrlich-Institute (PEI), which is responsible for blood products, biologicals and vaccines, and the Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM), which is responsible for all other medicinal products.

across agencies, as well as to use the quantitative data for statistical analyses together with the data collected within the written questionnaire.

The textual data from the interviews were categorized and summarized. The frequency of different categories of answers was counted. Parts of the interview data (mainly closed questions and numerical data) were analysed statistically with SPSS version 11.

2.3.2 Written agency survey

The written survey was sent out as an electronic form (MS-Excel sheet) to the agencies on 7 July 2004. All Agencies from EU Member States, EEA countries and EMEA participated in the survey. The last completed questionnaires were returned on October 28 and November 8, respectively.

The data were mostly submitted in electronic form. They were reviewed for completeness, eventual problems within the data were clarified, and the data were stored in an Excel database. From there they were imported into SPSS version 11, which was used to analyse statistically the survey data and parts of the interview data.

Different reporting rates were computed with the number of collected ADR reports related to the population size in the countries, but also to the type of products, (NAPs, MRPs, CAPs), to the value of pharmaceutical sales, and to the density of physicians in the country.

These reporting rates were correlated with various external criteria to evaluate their explanatory power (see two following tables). Spearman-rho correlation coefficients were calculated to account for unsymmetrical distributions which are very likely in studies like the present in which only a small number of cases (here: the 29 agencies) are available.

The criteria are population sizes from Eurostat, as well as figures on density of physicians, pharmaceutical sales, and the incidence of ADR-relevant diseases (age-standardized death rate; absolute numbers and per 100000) from WHO-Euro European health for all database (HFA-DB; source: http://data.euro.who.int; those numbers of 2002).

In our analysis the population of children was defined as ≤19 years of age, because only such data were available for all participating countries. However, the numbers of reports for "children" were probably counted for persons <18 years. Therefore, the computed reporting rates for children will underestimate the true value a bit.

The following table shows that the population-based reporting rates for 2003 and 2004 correlate with none of the external criteria except the 2003 population sizes. However, this is at least partially an effect of the small sample size of maximally 28 countries.

Table 2.4. Correlations of population-based reporting rates with external criteria

Correlation of … ↓	… with →	Physicians total per 100000 capita	Pharma-sales total per capita (in US$)	Incidence ADR-relevant diseases (absolute)	Incidence ADR-relevant diseases (per 100000 capita)
Reporting rate total 2003 per million capita	**Rho**	0.215	0.012	0.125	-0.147
	p	0.293	0.963	0.560	0.494
	N	26	17	24	24
Reporting rate total 2004 per million capita	**Rho**	0.066	-0.178	0.106	-0.116
	p	0.738	0.467	0.605	0.574
	N	28	19	26	26

Source: Fraunhofer ISI 2005

The rows "Rho" give the correlation coefficient for the reporting rates of 2003 and 2004 with the external criteria.

None of the correlations for the population-based reporting rates with the external criteria was significant on the 5%-level (row "p"); the same was true for the reporting rates for children (not presented). The rows market with an "N" contain the number of valid cases for which the single correlations could be computed.

To compute a reporting rate by dividing the absolute number of ADRs collected in a country by the number of inhabitants of this country means to control the reporting for the size of the population so that countries with different population sizes are comparable in the relative reporting rate. But, because the frequency of ADRs in a population can plausibly not only depend on the size of the population but will also vary with the number of physicians which can submit ADR reports, or with the volume of pharmaceutical products that are sold within a country, two other reporting rates were computed that seem to be more adequate than the one that is only based on the size of the population. These rates do not only control for the size of the populations, but the first also for the number of physicians and the second for the pharmaceutical sales; therefore they are more valid indicators for the functioning of the national pharmacovigilance systems than the population-based rate.

As the following table shows, the reporting rates based on pharmaceutical sales (row "Reporting rate total 2004 per sales in US$" as well as those based on numbers or physicians in the countries (row " Reporting rate total 2004 per physicians per 100,000 capita"), do not only correlate with the population size, but also with the WHO-figures on the absolute incidence of ADR-relevant diseases which the population-based indicator (row "Reporting rate total 2004 per million capita") does not. The correlation disappears for the relative incidence rate (Table 2.5).

Table 2.5. Correlations of sales-based reporting rates with external criteria

Correlation of … ↓	… with →	Physicians total per 100000 capita	Pharma-sales total per capita (in US$)	Incidence ADR-relevant diseases (absolute)	Incidence ADR-relevant diseases (per 100000 capita)
Reporting rate total 2004 per million capita	**Rho**	0.075	-0.244	0.025	-0.110
	p	0.720	0.362	0.911	0.617
	N	25	16	23	23
Reporting rate total 2004 per sales in US$	**Rho**	-0.009	0.288	0.756	0.503
	p	0.974	0.279	0.001**	0.047*
	N	16	16	16	16
Reporting rate total 2004 per physicians per 100,000 capita	**Rho**	0.168	0.312	0.517	-0.137
	p	0.423	0.240	0.012*	0.534
	N	25	16	23	23

Source: Fraunhofer ISI 2005; ** correlation significant on the 1%-level; * correlation significant on the 5%-level

The best reporting rate – measured by its correlation with the WHO incidence rates – is the reporting rate standardized at the pharmaceutical sales in the middle row. It has the highest absolute correlations of Rho=.76 with the absolute incidence and Rho=.50 with the relative incidence, and both of the correlations are significant or highly significant despite the small sample size. This reporting rate should be used for further analyses, as it also controls for different consumption patterns in the countries.

2.3.3 Delphi survey

2.3.3.1.1 Critical success factors

The preliminary list of critical success factors for the pharmacovigilance processes was submitted to the expert panel with the following question: "Relevance: How important is the factor for the performance of the European System for Pharmacovigilance (or parts of it)?"

Each factor was assessed according to the criteria

- Quality of the work
- Compliance with requirements,
- Speed ("kinetics"),
- Work load/costs,

on a five-point-rating scale (values: ++; +; 0; -; --). The values were explained as ++: strong positive influence; 0: not relevant; --: strong negative influence, and space was left for comments and for the indication and evaluation of additional important factors.

The following Figure 2.1 contains a part of the evaluation form. The full form including the aggregated values collected from the participants can be found in Annex 3.

Figure 2.1. Delphi survey form for the evaluation of success factors (part)

	Evaluation Round 1: Relevance for…																			
	… quality of the work					… compliance with requirements					… speed ("kinetics")					… work load/costs				
Success factor	**++**	**+**	**0**	**-**	**--**	**++**	**+**	**0**	**-**	**--**	**++**	**+**	**0**	**-**	**--**	**++**	**+**	**0**	**-**	**--**
1. … for Data collection																				
1.1 Comprehensiveness of the data																				
Mandatory reporting by HCPs	1						1						1				1			
Spontaneous reports from pharmacists	1						1						1				1			
Access to FDA data for national agencies		1					1						1					1		
Access to drug utilisation statistics	1					1						1						1		
Access to database of patients' medical records		1					1					1					1			
Highest-possible number of spontaneous reports			1					1					1				1			

Source: Fraunhofer ISI 2005

The evaluations by the survey participants in each cell of the table were summed up across the participants. Some of the success factors were not assessed by all participants. Therefore, to make the results comparable between indicators, percentages of answers in this cell of all answers were computed for each cell.

2.3.3.1.2 Performance indicators

The experts were asked either to complete an electronic form or to print and complete it manually. The form is presented in Figure 2.2.

Figure 2.2. Delphi survey form for the evaluation of performance indicators (part)

	Evaluation Round 1											
	Relevance				**Practicability**				**Interpretation**			
Performance indicator	**3**	**2**	**1**	**0**	**3**	**2**	**1**	**0**	**3**	**2**	**1**	**0**
1. ...for the input												
1.1 Comprehensiveness of the data												
Total number of ICSRs from your country received in last year		1					1				1	
Number of ICSRs from your country received in last year from MAHs				1		1						1
Number of ICSRs from your country received in last year direct from HCPs	1						1				1	
Number of ICSRs from your country received in last year direct from patients				1				1				1
Number of ICSRs from your country received in last year direct from pharmacists												
Number of ICSRs from your country received in last year direct from other HCPs												
Number of cases received/total number of ICSRs from your country												
% of serious ICSRs from your country		1					1			1		
% of ICSRs from your country as concerned MS		1					1			1		
% of ICSRs from your country as reference MS		1					1			1		
Number of PSURs received by origin and type of product			1			1					1	
Number of studies carried out on national database/ target number for database studies		1					1		1			

Source: Fraunhofer ISI 2005

The indicators were rated on three dimensions on rating scales with 4 values (see Table 2.6).

It was explained that some of the indicators would in their final version need combination with other indicators or relation e.g. to the size of the country in order to compute relative indicators or percentages.

Table 2.6. Criteria for the evaluation of indicators in the Delphi survey

Dimension/Explanation	Scale
Relevance:	
How important is the indicator to obtain a valid picture of the performance of the European System for Pharmacovigilance?	3: very relevant … 0: not relevant
Practicability:	
How easy is it to obtain the data for this indicator? We suppose that the data would have to be collected by the national agency or come from other sources. Please assume the availability of data in the country/region for which your agency is responsible in January 2006.	3: very easy to measure … 0: measurable only at very high costs
Interpretation:	
How easy is it to interpret the results?	3: very easy to interpret … 0: nearly not interpretable

Source: Fraunhofer ISI 2005

The evaluations by the survey participants in each cell of the table were summed up across the participants. Again, some of the indicators were not assessed by all participants. To make the results comparable between indicators, percentages of answers in this cell of all answers were computed for each cell.

3 System analysis and description of the status quo

In this section an overview of the European system of pharmacovigilance is provided It is structured in the following way: Section 3.1 describes the regulatory framework for pharmacovigilance. It is based on an overview provided by Professor Gassner from the University of Augsburg, Germany, and KKS-UKT. The implementation of the legal framework is reviewed in section 3.2, and important points from the systems in the USA, Japan and Canada are presented in paragraph 3.3.

The empirical approach to describe the status quo in the EU (including 25 EU Member States and EMEA) is based on personal interviews with representatives of the competent authorities, the supplementing questionnaire survey among agencies and on telephone interviews with additional stakeholders from industry, science and independent organisations on specific topics. The results from these work steps are presented in sections 3.4 to 3.8.

The results are presented as objectively as possible without an appraisal of the results by the authors.

Results of the Delphi process and the agency interviews also form the basis for the elaboration of critical success factors and performance indicators which were used to design the surveys; these steps will be presented in chapters 5 and 6, respectively. Then, the most important results from the case studies are presented (chapter 7) and some examples for best practice are given in chapter 8).

Pharmacovigilance is described as consisting of six phases:

- Data collection,
- Data management,
- Signal detection,
- Safety issue assessment,
- Decision-making,
- Communication and action to protect public health.

Besides this, general aspects are described in terms of

- Framework conditions, particularly the regulatory framework
- Resources for pharmacovigilance,
- Definitions and standards,
- General quality management,
- Outcomes.

3.1 Description of the regulatory framework of pharmacovigilance in Europe

In this section, the regulatory framework that shapes the functioning of the European pharmacovigilance system is presented.

3.1.1 Introduction

The European Medicines Agency defines pharmacovigilance as “the process of monitoring, evaluating and improving the safety of medicines in use. It is carried out by pharmaceutical companies on their products and by government agencies on all medicinal products. Healthcare Professionals (e.g. doctors and pharmacists) have a role too, in reporting suspected side effects of medicines to government agencies or pharmaceutical companies (EMEA 2005).

The World Health Organisation (WHO) defines pharmacovigilance as “the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problems”.

Pharmacovigilance activities include actions to detect and assess adverse drug reactions (ADR), evaluation of the probability of a causal relationship between the medicinal product and the adverse drug reaction, and actions taken in order to protect public health. This means e.g. the establishment of systems for the reporting of individual cases of adverse drug reactions to the supervising authority, discussion of safety problems within expert committees, the order of the Authorities for undertaking epidemiological safety studies or the change of the authorisation status of a medicinal product.

One of the objectives of the project “Assessment of the European Community System of Pharmacovigilance” is to describe the current system regarding the pharmacovigilance of marketed medicinal products for human use[6]. The legal framework of this system is based on the European pharmaceutical legislation, whose regulations are applicable on the Community level as well as on the level of the EU Member States (MS). The three other EEA Members Iceland, Liechtenstein and Norway have also joined this framework, and together with the central authorities and EU Member States they build the European system of pharmacovigilance. The actual application of the European legislation in the Member States varies, due to partly needed implementation of the European laws into the national legislation and due to the adjustment to the national conditions.

In the present report the legal framework of laws and guidance documents that has to be applied in the European system of pharmacovigilance is presented and examined. National laws of the Member States do not lie within the scope of this report.

3.1.2 Compilation and description of the relevant European laws and associated guidance documents

3.1.2.1 Legal framework of pharmacovigilance of marketed drugs

The interplay between national and EC authorities in the area of pharmacovigilance, in particular with respect to the actions that can be taken and the procedures applicable to the processing of safety concerns, depends on the type of marketing authorisation (Bendall 2004).

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6 The pharmacovigilance for veterinary medicinal products, which is not addressed here, is regulated in a quite similar manner.

Basically, there are two routes for marketing medicinal products throughout the EU: a centralised procedure at European level and a decentralised system at national level encompassing two types of authorisation procedures. A marketing authorisation for a medicinal product in more than one Member State must therefore be applied for through one of three procedures: either the “Centralised Procedure”, determined by Regulation (EC) No 726/2004, or the “Mutual Recognition Procedure” or the new “Decentralised Procedure”, regulated by Directive 2001/83/EC. Of course, national authorisations remain available for products to be marketed in one single Member State. Even purely national marketing authorisation procedures are, however, subject to harmonising provisions of Directive 2001/83/EC.

Centralised Procedure

The Centralised Procedure is administered by the EMEA. It consists of a single application which, when approved, grants marketing authorisation for all markets within the European Union (and the EEA).The European Commission is the responsible competent authority for the products which come to the market through the centralised procedure. This procedure is available to all new, or so-called “innovative” pharmaceuticals, and is obligatory for biotechnology-derived medicines and products containing new substances, for which the therapeutic indication is the treatment of several severe diseases.

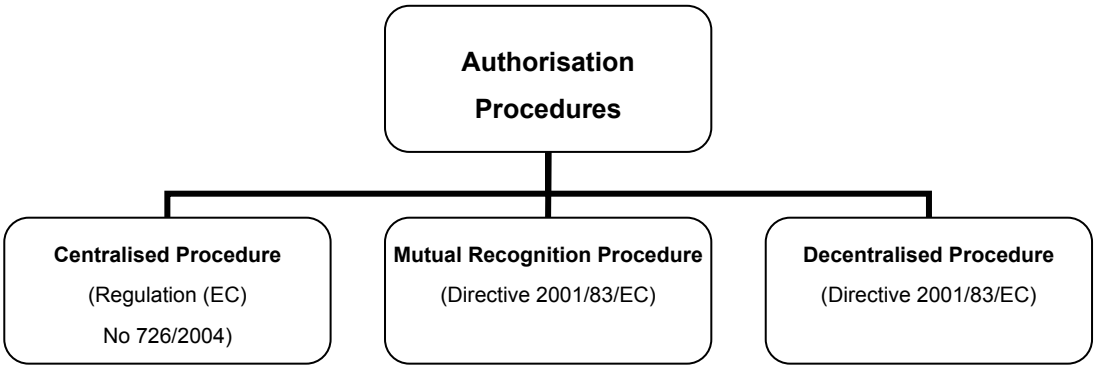
Mutual Recognition Procedure

Under this procedure the assessment and marketing authorisation of one Member State, the reference Member State, should be “mutually recognised” by other concerned Member States. Member States who recognise the first authorisation on the basis of the assessment report to be prepared by the reference Member State within 90 days, will grant a marketing authorisation with an identical summary of product characteristics. If a Member State raises objections and does not recognise the original marketing authorisation the matter may be referred for arbitration to the EMEA.

Decentralised Procedure

The new Decentralised Procedure is applicable in cases where an authorisation does not yet exist in any of the Member States. Identical dossiers will be submitted in all Member States where a marketing authorisation is sought. A reference Member State, selected by the applicant, will prepare draft assessment documents within 120 days and send them to the concerned Member States. They, in turn, will either approve the assessment or the application will continue into arbitration procedures.

Figure 3.1. Authorisation Procedures



The legal framework of pharmacovigilance for drugs marketed within the EU is specified mainly in Articles 21 to 29 of Regulation (EC) No 726/2004 with respect to centrally authorised medicinal products and in Articles 101 to 108 of Directive 2001/83/EC with respect to both decentrally and nationally authorised medicinal products. The Community has sought over the years to ensure that the pharmacovigilance systems for centrally authorised medicinal products and those authorised by other procedures become more and more consistent. Yet, there are some disparities and inconsistencies resulting from a non-optimal compliance of both national law and practice with the EC regulations.

The said basic legal texts are supplemented by Commission Regulation (EC) No 1085/2003 and Commission Regulation (EC) No 1084/2003, which describe the procedures that have to be followed in the case that an existing marketing authorisation of medicinal products on the European market has to be changed, further by Commission Regulation (EC) No 540/95 that regulates the procedures concerning “suspected unexpected non-serious adverse reactions”.

Additionally detailed instructions, definitions, standards and information regarding the precise conduct of pharmacovigilance related procedures are to be found in a number of guidance documents, first of all in “Volume 9 of the rules governing medicinal products in the European Union – Pharmacovigilance” and in the pharmacovigilance related guidelines of the International Conference on Harmonisation.

In the following sections, the regulatory state of the art is described in more detail.

3.1.2.1.1 Applicable European laws concerning centrally authorised medicinal products

Regulation (EC) No 726/2004

Council Regulation (EEC) No 2309/93 was replaced by Regulation (EC) No 726/2004.

Title II of Regulation (EC) No 726/2004 which includes the provisions relating to the pharmacovigilance of human drugs will apply from 20 November 2005.

Relevant information concerning pharmacovigilance are to be found in:

- Article 13 para 4, subpara 3 and article 16 para 2, subpara 2 and 3 (MHA's obligation for the provision of data concerning the sales, prescriptions and the benefit risk evaluation of a product to the EMEA)
- Articles 21 to 29 "pharmacovigilance" (tasks and procedures of the EMEA, responsibilities and procedures of the Marketing Authorisation Holder (MAH) and the Member States, reference to guidance document Volume 9 and to the data network of the Authorities, cooperation with the WHO)
- Articles 19 and 20 (control and execution procedures as to MAHs' obligation to fulfil the requirements laid down in Title IX of Directive 2001/83/EC)
- Article 57 para. 1 (c) to (f) (tasks of the EMEA)
- Article 67 para 4 (funding of activities relating to pharmacovigilance)

Figure 3.2. Regulation (EC) No 726/2004

REGULATION (EC) NO 726/2004
• applicable to centrally authorised medicinal products • Title II of the Regulation concerning, i.a., the pharmacovigilance of human drugs applicable with effect from 20 November 2005 • published in Volume 1 of "The rules governing medicinal products in the European Union": http://www.pharmacos.eudra.org/F2/eudralex/vol-1/home.htm

Commission Regulation (EC) No 540/95

- Commission Regulation (EC) No 540/95 complements Regulation (EC) No 726/2004.
- The Regulation lays down specific requirements for reporting non-serious unexpected adverse reactions.
- It is published in Volume 1 of "The rules governing medicinal products in the European Union": http://pharmacos.eudra.org/F2/eudralex/vol-1/home.htm.

Commission Regulation (EC) No 1085/2003

- Commission Regulation (EC) No 1085/2003 describes the procedures to be applied to change the marketing authorisation of centrally authorised medicinal products and to temporarily restrict their authorisation in case of emergency measures.
- It is published in Volume 1 of "The rules governing medicinal products in the European Union": http://pharmacos.eudra.org/F2/eudralex/vol-1/home.htm.

3.1.2.1.2 Applicable European laws concerning non-centrally authorised medicinal products

Directive 2001/83/EC

Directive 2001/83/EC constitutes the Community Code for medicinal products for human use marketed in the EU and authorised either in one single Member State or in more than one Member State under either the Mutual Recognition Procedure or the Decentralised Procedure.

The Directive was amended by Directive 2004/27/EC. This Directive should, i.e., step up pharmacovigilance and, more generally, market surveillance and sanctions in the event of failure to comply with the provisions. Furthermore, in the field of pharmacovigilance, account should be taken of the facilities offered by new information technologies to improve exchanges between Member States. The implementation into national law has to be completed no later than 30 October 2005.

The relevant information concerning pharmacovigilance and sanctions in the event of failure to comply with the provisions are to be found in:

- Article 1 „definitions“, in particular Article 1 Nos. 11 to 16
- Article 8(3)(ia) and 8(3)(n) (obligation of the applicant of a marketing authorisation concerning pharmacovigilance)
- Articles 23 paras. 1 and 3, 23a para. 3 “information obligations as regards marketed products”
- Articles 31, 32, 36 “Community referrals” (community interests, preconditions and procedure)
- Articles 101 to 108 „pharmacovigilance“ (tasks, responsibilities and procedures of the Member States and the EMEA, responsibilities and procedures of the MAH, reference to guidance document Volume 9 and to the data network of the Authorities)
- Article 111 “pharmacovigilance inspections”
- Articles 116, 117 „supervision and sanctions“ (responsibilities of the Member States)
- Articles 122, 123 (notification obligation of the Member States and of the MAH in case of changes of the authorisation status and emergency measures).
- Article 127a (Commission decisions on risk management)

Figure 3.3. Directive 2001/83/EC

DIRECTIVE 2001/83/EC
• Community Code for medicinal products for human use in the EU • applicable to nationally and non-centrally authorised medicinal products + some provisions are also relevant to centrally authorised products • sat last amended with respect to pharmacovigilance by Directive 2004/27/EC • published by the European Commission in Volume 1 of "The rules governing medicinal products in the European Union": http://www.pharmacos.eudra.org/F2/eudralex/vol-1/home.htm

Commission Regulation (EC) No 1084/2003

Commission Regulation (EC) No 1084/2003 describes the procedures to be applied to change the marketing authorisation of medicinal products that are authorised with the procedure of mutual recognition or that are subject of a referral (acc. to Articles 32, 33 and 34 of Directive 2001/83/EC) and to temporarily restrict their authorisation in case of emergency measures.

- The Regulation is published in Volume 1 of "The rules governing medicinal products in the European Union":

  http://www.pharmacos.eudra.org/F2/eudralex/vol-1/home.htm.

3.1.2.1.3 New Community legislation

The new Community legislation, coming into force in November 2005, will introduce additional tools to strengthen further the existing pharmacovigilance system in terms of communication quality and quantity. It comprises

- the submission of risk context data and, where appropriate, the description of the risk management system the applicant will introduce by applicants for a marketing authorisation;
- the collection of specific pharmacovigilance data for centrally authorised products from targeted groups of patients;
- the possibility for regulatory Authorities to take urgent provisional measures, for instance as a result of the evaluation of pharmacovigilance data;
- a reinforcement of the benefit/risk balance concept in the scientific assessment throughout the life cycle of medicinal products;
- a shorter Periodic Safety Update Report (PSUR) periodicity;

- a mandatory electronic reporting, save in exceptional circumstances, of ADRs by the National Competent Authorities (NCAs) and the MAHs;
- a strengthening of the enforcement through the possibility for financial penalties for pharmaceutical companies in case of non-adherence to the legal obligations.

Furthermore the new Community legislation concentrates on meeting the aim of transparency. Thus, e.g., the EudraVigilance database will be made accessible to Healthcare Professionals and the general public (Heads of Medicines Agencies 2005a; Moseley 2004).

3.1.2.2 Related guidance documents

Figure 3.4. Related guidance documents

RELATED GUIDANCE DOCUMENTS	
Volume 9 of the rules governing medicinal products in the EU • legal basis: Article 26 of Regulation (EC) No 726/2004 and Article 106 para. 1 of Directive 2001/83/EC • objective: giving guidance on the collection, verification and presentation of adverse drug reports • pharmacovigilance guidelines • no legal force yet binding in practical terms (EMEA 2004d) • published in Volume 9 of "The rules governing medicinal products in the EU": http://pharmacos.eudra.org/F2/eudralex/vol-9/home.htm	*ICH/CHMP Guidelines* • European Commission – represented by the CHMP of the EMEA – adopted 6 Guidelines of the ICH • objective: achievement of greater harmonisation in the interpretation and application of technical guidelines and requirements • scientific guidelines • no legal force yet binding in practical terms (EMEA 2004d).

3.1.2.2.1 "Volume 9 of the rules governing medicinal products in the European Union" – Pharmacovigilance

This document is drawn up by the European Commission in consultation with the EMEA, Member States and interested parties in accordance with Article 26 para. 1 of Regulation (EC) No 726/2004 and Article 106 para. 1 of Directive 2001/83/EC to give "guidance on the collection, verification and presentation of adverse reaction reports in order to facilitate the exchange of information about pharmacovigilance (of authorised medicinal products for human use and veterinary medicinal products) within the Community (Eudralex Volume 9, Pharmacovigilance Guideline, No. 1 2004). The current version of Volume 9 dates from June 2004. This version is actually being updated to reflect the new legislation.

Volume 9 comprises 4 parts with the following content:

- Part I „Guidance and Procedures for Marketing Authorisation Holders" and „Guidance and Procedures for Competent Authorities" describes in detail the tasks, obligations and procedures of the two main responsible parties in the field of pharmacovigilance and gives concrete guidance, definitions and standards for the performance of all relevant processes.
- Part II deals with pharmacovigilance of veterinary medicinal products.
- Part III "EU Electronic Exchange of Pharmacovigilance Information" describes the technical requirements for the electronic exchange of pharmacovigilance related information in the Community and references to the agreed terminology.
- Part IV "Reference Legislative and Administrative Information" refers in general to legal information and in particular to ICH Guidelines E2B(M) and E2C (with E2C addendum) that are integrated in Volume 9.

3.1.2.2.2 ICH/CHMP guidelines

The EU, through its representation on the ICH Steering Committee and through subsequent adoption of ICH guidelines by the Committee for Medicinal Products for Human Use (CHMP) of the EMEA, has adopted six tripartite guidelines of the International Conference on Harmonisation (ICH) relating to pharmacovigilance. ICH guidelines are also incorporated into Volume 9 when this volume is updated. ICH Guidelines serve "to achieve greater harmonisation in the interpretation and application of technical guidelines and requirements" (International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) 2005) by the development and the use-application of medicinal products. They represent the international standard regarding definitions, formats and technical requirements.

The adoption of ICH Guidelines through the CHMP and Volume 9 has as a result that the international standards described in the guidelines have to be adhered to within the EU regarding pharmacovigilance related processes. These guidelines are, however, not legally binding in a strict sense.

The guidelines explicitly refer to definitions, management and expedited reporting of individual adverse reaction cases, including electronic formats, periodic reporting of worldwide safety data and planning of pharmacovigilance activities (Arnold 2004).

ICH Guideline E2A (CPMP/ICH/377/95)

- Title: Clinical Safety Data Management: Definitions and Standards for Expedited Reporting
- This guideline came into operation in June 1995.
- The guideline is published under

http://www.emea.eu.int/pdfs/human/ich/037795en.pdf

Figure 3.5. Key points guideline E2A

KEY POINTS GUIDELINE E2A (Bahri and Tsintis 2005d})
• Definitions for adverse event (AE) and adverse drug reaction (ADR) in the pre-authorisation phase
• Criteria for serious AE/ADR
• Expectedness of an AE/ADR based on clinical observations and its documentation in the applicable product information
• Causality assessment as good case practice for AE/ADR cases from clinical trials
• Implied possible causality for spontaneously reported ADR cases
• Standards for expedited reporting from clinical trials
• Definition of minimum case report information for report submission to authorities
• Follow-up reporting
• Unblinding procedures for serious ADRs
• Reporting of emerging information on post-study ADRs
• Reporting requirement for active comparator

ICH Guideline E2B(M) CPMP/ICH/287/95

- Title: Clinical Safety Data Management: Data Elements for Transmission of Individual Case Safety Reports
- This guideline came into operation in November 2000 with minor editorial changes in March 2001.
- The guideline is published under http://www.emea.eu.int/pdfs/human/ich/028795en.pdf

Figure 3.6. Key points guideline E2B(M)

KEY POINTS E2B(M) GUIDELINE (Bahri and Tsintis 2005)
• Description of all data elements of ADR case reports: title and content of each data field
• Technical specifications such as field length and field value for each of the data fields and the related additional technical data fields
• List of abbreviations for units
• List of units for time intervals
• List of routes of administrations

ICH Guideline E2C (CPMP/ICH/288/95)

- Title: Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs
- This guideline came into operation in June 1997.
- The guideline is published under http://www.emea.eu.int/pdfs/human/ich/028895en.pdf.

Figure 3.7. Key points guideline E2C

KEY POINTS E2C GUIDELINE (Bahri and Tsintis 2005)
• Inclusion of all product presentations on one PSUR
• Concept of international birth date of a product, determining the data lock points of PSURs
• Provision to submit a set of PSURs, each covering subsequent 6 months, to facilitate PSUR submission acc. to local frequency
• Description of all data sources to be covered in a PSUR
• Inclusion of worldwide information on marketing authorisation status and regulatory safety-related action, ADR and exposure data
• Use of company core safety information (CCSI) as reference and concept of unlistedness of an ADR (i.e. unlisted in comparison to the CCSI versus unexpected in comparison to local authorised product information)
• Presentation of individual case history
• Formats of ADR line-listings and summary tabulations
• Presentation of exposure data
• Overall safety evaluation and conclusion: analysis and discussion of data by MAH with view to possible safety-related action
• Explanation on responsibilities of MAHs in contractual relationship
• Annex of medically unconfirmed ADR case reports to be submitted as requested locally

ICH Guideline E2C Addendum (CPMP/ICH/4679/02)

- Title: Addendum to ICH E2C: Clinical Safety Data Management, Periodic Safety Update Reports for Marketed Drugs
- The E2C addendum guideline is in operation since August 2003.
- The guideline is published under http://www.emea.eu.int/pdfs/human/ich/467902en.pdf.

Figure 3.8. Key points guideline E2C Addendum

KEY POINTS E2C ADDENDUM GUIDELINE (Bahri and Tsintis 2005)
• Clarification regarding inclusion of all product presentations in one (PSUR) • Executive summary as new part of the PSUR • New statement of proprietary information to be included in PSUR • Use of reference safety information in relation to time periods covered by PSUR • Further guidance on presentation of exposure data • Organisation of some PSUR parts by system organ class • Risk management programmes, if in place for the product, to be discussed in PSUR • Separate benefit-risk analysis, if conducted recently for the product, to be discussed in PSUR • Recommendations for PSUR submission during transition period of harmonisation towards international birth date; clarifications for such harmonisation • Clarification on restart of PSUR submission frequency • New concept of summary bridging report supporting submission a set of covering 6 mths/PSUR • New concept of addendum report to cover the period between last PSUR and local MAH renewal date

ICH Guideline E2D (CPMP/ICH/3945/03)

- Title: Post Approval Safety Data Management
- This guideline came into operation in May 2004.
- The guideline is published under http://www.emea.eu.int/pdfs/human/ich/394503en.pdf.

Figure 3.9. Key points guideline E2D

KEY POINTS E2D GUIDELINE (BAHRI AND TSINTIS 2005)
• Definitions for AE and ADR in the post-authorisation phase • Criteria for serious AE/ADR in accordance with ICH-E2A • Expectedness of an ADR based on clinical observation and its documentation in the authorised product information; explanations regarding class effects • Differentiation between sources of unsolicited and solicited reports • Explanation on stimulated (but unsolicited) reporting • Standards for expedited reporting in post-authorisation phase • Definition of minimum case report information for report submission to authorities with explanations • Follow-up reporting • Lack of efficacy reporting needs • Guidance on ADR narratives • Guidance on ADR case assessment • Management of cases of exposure during pregnancy • Explanation on reporting responsibility of MAH despite any contractual relationship in place

ICH Guideline E2E (CPMP/ICH/5716/03)

- Title: Pharmacovigilance Planning (PVP)
- This guideline has come into operation in June 2005.
- The guideline is published under http://www.emea.eu.int/pdfs/human/ich/571603en.pdf.

Figure 3.10. Key points guideline E2E

KEY POINTS E2E GUIDELINE (BAHRI AND TSINTIS 2005)
• Elements for pharmacovigilance specification as summary of identified risks, the risks potentially arising from populations and situations which have not yet been adequately studied and potential other risks • Format of a pharmacovigilance plan based on the specification • Within the pharmacovigilance plan, description of routine pharmacovigilance as minimum and inclusion of a safety action plan for specific issues/missing information as needed • Format of safety action plan, with description of rationale for action and timetable for evaluation and reporting ('milestones') • Possible synchronisation of timetable with regulatory timetable for post-authorisation assessment, such as PSUR assessment or marketing authorisation renewal assessment • Principles for design and conduct pharmacoepidemiological studies of non-experimental design with references to international guidelines • Overview of methods for data collection to investigate the known or unknown risks and references

3.1.2.3 Legal basis of pharmacovigilance in clinical trials

For all those medicinal products which are being applied in clinical trials (that includes clinical trials performed to collect safety data) the relevant regulations to pharmacovigilance are to be found in Articles 11, 16, 17 and 18 of Directive 2001/20/EC (implementation of Good Clinical Practice in the conduct of clinical trials on medicinal products for human use). All medicinal products used in clinical trials come under this Directive, regardless of their authorisation procedure (centralised, not centralised) or whether they are marketed or not.

The Directive was adopted in May 2001. It shall have been implemented into national law at the latest with effect from 1 May 2004.

The Directive is published in Volume 1 of "The rules governing medicinal products in the European Union":

http://pharmacos.eudra.org/F2/eudralex/vol-1/home.htm.

More details regarding definitions and processes relevant to pharmacovigilance, which are applicable in clinical trials, are to be found in two guidance documents published by the Commission pursuant to Articles 11, 16, 17 and 18 of Directive 2001/20/EC „Detailed guidance on the collection, verification and presentation of adverse reaction reports arising from clinical trials on medicinal products for human use" and „Detailed guidance on the European database of Suspected Unexpected Serious Adverse Reactions (Eudravigilance – Clinical Trial Module)".

The documents are published under
http://pharmacos.eudra.org/F2/pharmacos/dir200120ec.htm.

3.1.3 Relevant stakeholders involved in the pharmacovigilance process

The wide spectrum of persons and institutions, who are involved in the field of medicinal products, starting with the manufacturers and the MAHs, up to the patients and the safety monitoring Authorities, who are in charge of protecting public health, results in a great number of stakeholders, who are actively involved in this process.

The responsible organs for pharmacovigilance – the Authorities of the Member States, the EMEA, the European Commission and the MAH of a medicinal product, their responsibilities and obligations are explicitly described in the European pharmaceutical legislation and the associated guidance documents.

Furthermore Healthcare Professionals (HCPs), patients, distributors and addressees of information and actions relevant to pharmacovigilance are included.

The obligations of the stakeholders, which are explicitly stated in the European laws and guidelines, are presented below:

3.1.3.1 Member States

The Member States are obliged to operate a pharmacovigilance system.

MS encourage doctors and other HCPs to report suspected adverse reactions to the NCAs. Furthermore, they impose specific requirements on doctors and other HCPs in respect of the reporting of suspected serious or unexpected adverse reactions.

They should have at their disposal sufficient personnel and infrastructure, in order to ensure the conduct of pharmacovigilance.

3.1.3.2 Competent authorities and institutions

3.1.3.2.1 Preliminary note

Main actors in pharmacovigilance matters regarding the protection of public health are several Authorities and institutions in the EU.

Due to the different legislations for medicinal products on the European market more than one authority is responsible for the regulatory affairs.

3.1.3.2.2 The National Competent Authorities

The NCAs in the Member States are responsible for nationally authorised products including products that are decentrally authorised. For this case the responsibility for the conduct of pharmacovigilance including the implementation of regulatory actions rests with the NCAs of all Member States that have granted a marketing authorisation.

The NCAs continually monitor the safety profile of the products available on their territory and take appropriate actions where necessary and monitor the compliance of MAHs with their obligations with respect to pharmacovigilance. The NCAs are also responsible for the communication with the MAH. In order to avoid duplicate effort the Member States have agreed that the reference Member State as the Member State that was leading in the process of the decentralised marketing authorisation takes a leading function on all activities of pharmacovigilance. With re-

spect to centrally authorised products the Member States are responsible to monitor medicinal products within their respective territories and act as the supervisory authorities. However, the rapporteur that had a leading function in allocating the marketing authorisation takes also a lead in pharmacovigilance, unless otherwise decided by the CHMP (Moseley 2004).

3.1.3.2.3 The European Commission

The European Commission has overall responsibility for the EU system of pharmacovigilance including policy and EU law.

The Commission is the Competent Authority in the case of centrally authorised products and is responsible for the adoption of decisions based on opinions of the CHMP relating to these products. As regards decentrally authorised medicines the Commission is responsible to adopt decisions based on opinions of the CHMP for those products that are subject to the referral procedures (Moseley 2004).

Furthermore it shall draw up guidelines on the collection, verification and presentation of adverse reaction reports, including technical requirements for electronic exchange of pharmacovigilance information in accordance with internationally agreed formats, and shall publish a reference to an internationally agreed medical terminology.

3.1.3.2.4 The EMEA

Acc. to Article 57 para. 1 (c) of Regulation (EC) No 726/2004 one of the tasks of the EMEA is “to coordinate the supervision… of medicinal products which have been authorised within the Community and to provide advice on the measures necessary to ensure the safe and effective use of these products, in particular by evaluation, coordination of the implementation of pharmacovigilance obligations and the monitoring of such implementation”.

The Agency secretariat coordinates the pharmacovigilance related processes (including Member States’ pharmacovigilance activities), gives advice on necessary safety measures and provides information about adverse reactions through a database. It is also responsible for the communication with the MAHs of centrally authorised products and for coordination of issues relating to the monitoring of the compliance of the MAH with its pharmacovigilance obligations (Moseley 2004).

3.1.3.2.5 The CHMP

The EMEA’s scientific committee, the CHMP, is responsible for providing scientific advice evaluating evidence and formulating opinions on emerging safety issues of centrally authorised products and of products that are subject of a referral (Moseley 2004).

3.1.3.2.6 The Pharmacovigilance Working Party

The principal task of the CHMP’s Pharmacovigilance Working Party (PhVWP) is “to provide advice on the safety of medicinal products authorised in the European Union (EU) and the investigation of adverse reactions to enable effective identification, assessment and management of risk, at any phase in the product life cycle. On the basis of such advice the PhVWP will provide, where applicable, recommendations for regulatory action to its stakeholders, i.e. the CHMP/EMEA and NCAs” (EMEA 2004c).

Acc. to this document the key responsibilities of the PhVWP are:

- evaluation of potential signals arising from spontaneous reporting, including those identified from the EudraVigilance database, and all other sources, including epidemiological databases, studies and published literature;
- provision of advice on confirmation and quantification of risk and on regulatory options;
- risk management by advising on risk management plans;
- monitoring regulatory action and the outcomes of such action;
- setting standards for procedures and methodologies to promote good vigilance practice;
- promotion of communication and exchange of information between the EMEA and NCAs;
- international cooperation.

3.1.3.3 Marketing authorisation holders

MAHs are primarily responsible for the safety of their medicinal products, from the start of drug development and throughout the lifecycle of a product.

"The MAH has to fulfil various pharmacovigilance system requirements which are either explicitly laid down in legislation or are detailed in supporting guidelines" *(*EMEA 2001).

The responsibility for the safety of the individual medicinal products rests with the MAH. He is obliged to establish and operate a system, which allows the conduct of all obligations that derive from the ongoing safety monitoring of the medicinal product.

Figure 3.11. Key requirements to the pharmacovigilance systems of MAHs

SUMMARY OF PHARMACOVIGILANCE SYSTEM REQUIREMENTS OF THE MAHS (EMEA 2001)
• expedited reporting • periodic safety update reporting • responding to requests for information from Competent Authorities • handling of urgent safety restrictions and safety variations • continuous monitoring of the safety profile of the authorised medicinal product • notifying Competent Authorities and health professionals of changes to the risk-benefit profile of products • meeting commitments made at the time of authorisation • internal audit of the pharmacovigilance system

3.1.3.4 Health care professionals and patients

Medical specialists, doctors, nurses, pharmacists and others (depending on the Member States' regulations) constitute the group of the HCPs. They have direct contact to the patients and they possess medical knowledge. Therefore, they are an important source for the collection of safety data, which arise from the application of medicinal products.

Moreover, HCPs are responsible to inform the patients about safety related problems and changes of the application of a medicinal product. Thus, the practical implementation of pharmacovigilance and the prescription of a safe treatment rest with them.

3.1.4 Pharmacovigilance related main processes and required infrastructure

3.1.4.1 General conditions

According to European law both the Regulatory Authorities and the MAHs have to provide the on-going supervision of the safety of medicinal products marketed in the Community. To grant this task both parties are required to establish appropriate systems.

The systems have to fulfil the following tasks (Eudralex 2005):

1. Collection and management of data relevant to medicines' safety
2. The detection of new or changing 'signals' of medicines safety issues
3. Assessment and decision making with regard to safety issues
4. Action (including regulatory action) to protect public health
5. Communication / transparency with stakeholders ·
6. Audit, both of the outcomes of actions taken and of the key processes involved.

3.1.4.2 Collection and management of data relevant to medicines safety

3.1.4.2.1 Collection of data relevant to medicines safety

Competent Authorities, MAHs and HCPs/consumers contribute to the collection of pharmacovigilance relevant data.

Figure 3.12. Overview of processes in collection of data relevant to medicines safety

DATA SOURCES	HCPS/ CONSUMERS	MAHS	AUTHORITIES
Spontaneous adverse reaction reports	• Generating • Reporting	• Mandatory collection • Mandatory reporting	• Mandatory collection • Mandatory reporting
PSURs	–	• Preparation	• Assessment
Published sources and literature	–	• Mandatory enquiry	• Mandatory enquiry
Systematic data collection / studies	–	• Initiation • Performance	• Initiation • Performance

3.1.4.2.2 Transmission of spontaneous adverse reaction reports

Stored and evaluated spontaneous reports have to be transmitted from the MAH to the Authorities and between the Authorities. To simplify the data exchange the EMEA has set up a data network that can be used by MAHs and the Authorities to send a report and by the Authorities to retrieve the information simultaneously.

According to ICH E2D and ICH-E2A the classification of a report determines its forwarding as expedited or not expedited.

3.1.4.2.3 Involved authorities

The Member States authorities

The expedited reporting

Competent Authorities of the Member States are obliged to evaluate and transmit reports. Format and content shall comply with E2A and E2B.

The following figure summarises the expedited reporting by the Member States' Authorities:

Figure 3.13. Expedited reporting obligations by MS Authorities

COLLECTION	TRANSMISSION TO
• Reports of suspected serious adverse reactions occurred within the territory of the Member State (transmitted by Healthcare Professionals and the MAH)	• MAH • EMEA • WHO (according to guidance on "Principles of Providing the WHO with pharmacovigilance information" (Eudralex Volume 9, Pharmacovigilance Guideline, No. 7 2004) • Entry into the EudraVigilance database
• EU reports of suspected serious adverse reactions transmitted by the EMEA	• No transmission
• Reports of suspected unexpected serious adverse drug reactions/occurred outside EU and authorised in the Member State / transmitted by the MAH	• No transmission

Pharmacovigilance tools and resources

In general the established pharmacovigilance systems of the Member States should provide the collection and scientific evaluation of data relevant for the pharmacovigilance of medicinal products.

In order to achieve this, the Member States need a sufficient number of scientifically qualified staff to ensure that the collection, evaluation and transmission of relevant information for decision-making processes and for the implementation of necessary actions according to scientific standards is possible in required amount and time.

Additional work of personnel of the Member States in different expert committees on EC level (e.g. CHMP) has to be taken into account in this calculation.

Sources of pharmacovigilance relevant data

All Member States are obliged to search relevant literature and evaluate PSURs and reports of performed Post-authorisation Safety Studies (PASS) for medicinal products that are authorised in their territory. The latter includes an overall-risk-benefit analysis and the preparation of assessment reports that are to be transmitted to the Authorities of those Member States where the medicinal product is authorised. In the case of centrally authorised medicinal products the reports have to be transmitted additionally to the EMEA.

For centrally authorised medicinal products the assessment of the PSURs / reports of PASS is performed by the rapporteur (or the chosen substitute). For decentrally

authorised drugs the reference Member State (or the chosen substitute) analyses the reports for all concerned Member States.

The EMEA

The expedited reporting

EMEA is obliged to collect and transmit reports. Format and content shall comply with E2A and E2B.

The following table summarises the expedited reporting by the EMEA:

Figure 3.14. Expedited reporting by the EMEA

COLLECTION	TRANSMISSION TO
• All reports of serious adverse drug reaction / occurred within the EU / transmitted by NCAs	• All reports of serious adverse drug reactions of centrally authorised products to the NCAs
• All reports of suspected unexpected serious adverse drug reactions / occurred outside EU and authorised in the EU / transmitted by NCAs and MAHs	• Entry into the EudraVigilance database

EudraVigilance

EMEA has established a data network in cooperation with the Member States and the European Commission for safe and fast electronic exchange of data between the Authorities with the following levels of information: transmission of simple messages and free text documents (e.g. assessment reports or routine contacts), exchange of aggregate information as described for the Rapid Alert System (RAS) and the Non Urgent Information System (NUIS) (see below 4.2.3.3.), exchange of cumulative information, exchange of single case data via EudraVigilance. This data-processing network and management system was launched in December 2001. It has been developed according to internationally agreed standards. EudraVigilance is regarded as one of the main pillars of the European Risk Management Strategy.

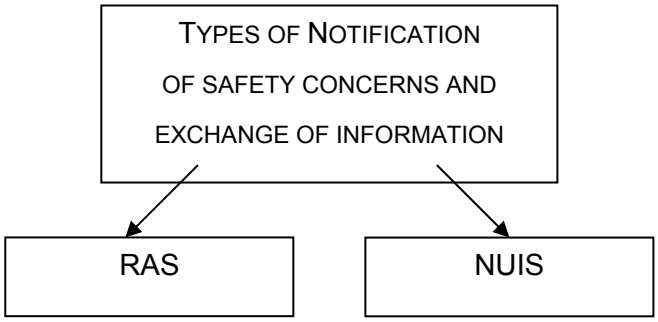
The Authorities have to dispose of sufficient and appropriate electronic databases and have to ensure that for electronic transmission of ICSRs and PSURs the following guidelines and specification can be fulfilled: ICH Guidelines E2A / E2B / E2C / M1/ M2. Deadline for establishment and functioning of the system of electronic transmission of ICSRs of centrally authorised medicinal products is 20 November 2005.

Communication between the authorities

In the framework of the European laws the communication between the Authorities of the Member States with the EMEA and the European Commission is described in detail in the first place by Volume 9 (Eudralex Volume 9, Pharmacovigilance Guideline, No. 2 2005).

Besides the transmission of adverse reaction reports the information exchange between Authorities and the discussion of detected safety issues that could lead to a change in the risk-benefit-balance of the product is central to this communication. In order to be able to process information immediately in urgent cases, the Authorities maintain the Rapid Alert System (RAS) and the Non Urgent Information System (NUIS). The basis of the system is EudraNet, a secure intranet established by the EMEA, through which the data can be transmitted electronically.

Figure 3.15. Types of notification of safety concerns and exchange of information



"The purpose of the RAS is to alert, with the appropriate degree of urgency, other Member States, EFTA countries concerned, the Agency and the European Commission about pharmacovigilance data related to medicinal products which indicate that action could be needed urgently to protect public health. It is essential that the communication of such problems occurs at an early stage, normally before a decision is taken in a Member State".

The RAS should be used when a Member State is concerned about a change in the balance between risks and benefits of a medicinal product that could require major changes with respect to the validity or the content of the marketing authorisation such as:

- the urgent variation, suspension or withdrawal of the marketing authorisation, the recall of the medicinal product from the market;
- changes in the SPC such as
  - the introduction of new contraindications,
  - the introduction of new warnings,
  - the reduction of the recommended dose,
  - the restriction in the indications,
  - the restriction in the availability of the medicinal product;
- the need to inform health care professionals or patients about an identified risk without delay.

The NUIS is a procedure established to support the collection and exchange of pharmacovigilance information between the Competent Authorities of Member States, the EC and the EMEA, which does not fulfil the criteria for a Rapid Alert. The NUIS refers, i.e., to

- pharmacovigilance data which do not require immediate or urgent action and/or where additional information is required from other Member States to support the evaluation of a potential concern,
- the provision of pharmacovigilance information not requiring a response.

3.1.4.2.4 The marketing authorisation holder

The expedited reporting

MAHs are obliged to collect, evaluate and transmit adverse reaction reports (acc. to Article 104 para. 1-5 of Directive 2001/83/EC and Article 24 para. 1-2 of Regulation (EC) No 726/2004). Format and content shall comply with E2A and E2B.

The following table summarises their expedited reporting:

Figure 3.16. Expedited reporting by MAHs

COLLECTION	TRANSMISSION TO
All reports of suspected serious adverse reactions/occurred in the EU/ spontaneously reported by Healthcare Professionals	• To the Competent Authorities in the Member States in whose territory the incident occurred • Additionally to the reference Member State in the case of decentrally authorised products and products that have been subject of a referral
Reports of suspected serious adverse drug reactions / occurred in the EU / of which the MAH can reasonably be expected to have knowledge	
Reports of suspected serious adverse reactions transferred from Member States Authorities	• No transmission
All reports of suspected unexpected serious adverse reactions / occurred outside EU / spontaneously reported by Healthcare Professionals	• All Member States where the medicinal product is authorised • EMEA

Sources of relevant pharmacovigilance data: The PSUR

The MAH is legally obliged to provide information on adverse effects of a medicinal product in the form of a Periodic Safety Update Report (PSUR) immediately on demand or in legally defined intervals to the Authorities that have granted a marketing authorisation (according to Article 104 para. 6 of Directive 2001/83/EC, Article 24 para. 3 of Regulation (EC) No 726/2004).

Format and content of this report shall comply with ICH Guideline E2C, E2C addendum.

The PSUR represents the world-wide safety experience of a medicinal product. It contains all relevant new safety information from appropriate sources, data to patient exposure, the summary of the market authorisation status in the different countries and any significant variations of the marketing authorisation due to safety issues.

The PSUR, regulated in Directive 2001/83/EC, was modified by Directive 2004/27/EC that contains the following amendments:

- The reports of all adverse reactions shall be submitted to the Competent Authorities in the form of a PSUR, immediately upon request or at least every six months after authorisation and until the placing on the market.
- PSURs shall also be submitted immediately upon request or at least every six months during the first two years following the initial placing on the market and once a year for the following two years. Thereafter, the reports shall be submitted at three-yearly intervals, or immediately upon request.
- Finally they shall include a scientific evaluation of the risk-benefit balance of the medicinal product.

Other sources of relevant pharmacovigilance data

- Relevant medical literature due to the obligation to screen it weekly (Rosenberger and Schaefer 2003);
- Data sources specified in the framework of Article 8 para. 3 lit. ia of Directive 2001/83/EC requested pharmacovigilance system or risk management system;
- Pharmacovigilance data generated in specific investigations requested by the EMEA according to Article 26 para. 3 of Regulation (EC) No 726/2004.

Required staff

Required by Directive 2001/83/EC the MAH has to name permanently and continuously a qualified person experienced in pharmacovigilance himself or that is advised by medical experts that execute the activities of the MAH being relevant for the pharmacovigilance by respecting the given time limits. The qualified person shall reside in the Community.

Figure 3.17. The responsibilities of the qualified person

THE RESPONSIBILITIES OF THE QUALIFIED PERSON
• establishment and maintenance of a system which ensures that information about all suspected adverse reactions which are reported to the personnel of the company, and to medical representatives, is collected and collated in order to be accessible at least at one point within the Community; • preparation for the Competent Authorities of the reports of all suspected adverse reactions occurring either in the Community or in a third country • ensuring that any request from the Competent Authorities for the provision of additional information is answered fully and promptly; • provision of any other information to the Competent Authorities relevant to the evaluation of the benefits and risks afforded by a medicinal product, including appropriate information on PASS.

IT-infrastructure

The MAH has to guarantee that for the electronic transmission of ICSRs and PSURs the following guidelines and specification will be respected: ICH Guidelines E2A / E2B / E2C / M1 / M2.

Deadline for establishment and functioning of the system of electronic transmission of ICSRs of centrally authorised medicinal products is 20 November, 2005.

3.1.4.2.5 The healthcare professionals

Primary reporting of spontaneous adverse reaction reports

Healthcare Professionals send spontaneously adverse drug reaction reports to the MAH or to the Authorities. Patients are encouraged to report suspected ADRs to their healthcare professional. The Member States are required to take measures to support this procedure and in particular the reporting to the Competent Authorities (Article 101 of Directive 2001/83/EC).

In particular, Authorities should communicate the importance of these reports towards the HCPs, implement a user friendly communication system with acknowledgment messages and feed back and inform regularly or in case of emergency on safety issues.

Communication of authorities with healthcare professionals

Safety issues of a medicinal product that up to now were not known and not described in the SPC or changes in the marketing authorisations have to be communicated to the HCPs or directly to the public. For this the Authorities have the following possibilities: they can change the product information, forward information on adverse reactions in official bulletins / newsletters or they can initiate a so-called Dear-Doctor-Letter (that is mostly prepared by the MAH). In some exceptional

cases co-ordinated press releases may be necessary of safety issues, information may also be reported in the media.

For drugs that are subject to the European pharmaceutical legislation it is necessary that the information to HCPs or the public is carefully coordinated in time and content, since there will be always several Member States affected (Eudralex Volume 9, Pharmacovigilance Guideline, No. 3 2005).

3.1.4.3 The detection of new or changing 'signals' of medicines safety issues

All safety relevant data and in particular all spontaneous reports are to be searched at regular intervals in order to detect signals, i.e. up to now unknown relationships between a medicinal product and an adverse drug reaction. This can be done by checking in a qualitative way the reports in a case by case analysis of the reports by trained personal or analysing automatically quantitative effects of reports that are stored in an electronic data base, evaluation of PASS and clinical trials and screening of published sources and literature (Waller 2004).

3.1.4.3.1 Identification of possible signals

- The following parties are responsible for signal detection (Eudralex Volume 9, Pharmacovigilance Guideline, No. 4 2004; Arlett 2001): MAH: Signals arising of its own products
- NCAs: Signals arising from information in their territory
- Reference Member State: Signals arising from information about decentrally authorised products under its observation
- Rapporteur: Signals arising from information about centrally authorised products under its observation
- Agency secretariat: Signals arising from information about centrally authorised products in agreement with the rapporteur

3.1.4.3.2 Communication about detected signals

Competent Authorities and the MAH should inform each other about identified signals, which may impact the risk-benefit-profile of a medicinal product (Eudralex Volume 9, Pharmacovigilance Guideline, No. 5 2004).

3.1.4.4 Assessment and decision making with regard to safety issues

The MAH is responsible for the evaluation of safety issues and subsequent decisions concerning his own products.

Due to the legal obligation to monitor and control the authorisation of medicinal products the Competent Authority, which has a leading function in the processing of the pharmacovigilance relevant activities, i.e. the reference Member State and the rapporteur, unless otherwise decided, is responsible for the assessment of safety issues arising on signals, PSURs and otherwise reports and for the preparation of assessment reports (Eudralex Volume 9, Pharmacovigilance Guideline, No. 6 2004; EMEA 2004b; Moseley 2004).

3.1.4.4.1 Decentrally authorised products

Responsible for the assessment of safety issues is the reference Member State, which also decides about the need of additional scientific advice, given by the PhVWP. The PhVWP makes non-binding recommendations about regulatory actions. In agreement with the concerned Member State the reference Member State prepares an assessment report with recommendation of regulatory actions. The Competent Authorities are responsible for the implementation of the recommended regulatory action in their MS.

In the following situations the CHMP must be involved in the assessment of safety issues by the reference Member State:

- in the conduction of referrals according to Articles 31, 36, 37 of Directive 2001/83/EC;
- consideration to suspend, revoke or vary the marketing authorisation (Article 107 para. 2 subpara. 2 of Directive 2001/83/EC);
- suspension of the marketing authorisation in the case of an urgent action to protect public health (Article 107 para. 2 subpara. 2 of Directive 2001/83/EC);
- optional on request of a MS during variation procedure (Article 107 para. 2 subpara. 3 of Directive 2001/83/EC).

The CHMP adopts opinions with recommendations of regulatory actions, the European Commission formulates decisions on these. The competent authorities of the MS are responsible for the implementation of the actions following the decision.

3.1.4.4.2 Centrally authorised products

The rapporteur is responsible for the assessment (including the preparation of reports) of safety issues concerning centrally authorised products. He also decides about the need of additional scientific advice by the PhVWP. The PhVWP gives non-binding recommendation for regulatory actions. The rapporteur refers assessment reports and recommendations to the CHMP. The CHMP adopts opinions with regulatory actions in the case of safety issues that require changes of the marketing authorisation concerning centrally authorised products (Article 5 para. 2 of Regulation (EC) No 726/2004). The European Commission formulates the decision which is then binding on the Member States.

3.1.4.5 Action (including regulatory action) to protect public health

In general action can be caused compulsorily by NCAs or voluntarily by MAHs in accordance with the legislation.

3.1.4.5.1 Regulatory actions by NCAs

The following safety issues can trigger major regulatory actions of the NCAs (Articles 116, 117 of Directive 2001/83/EC)

1. Product is harmful under the normal conditions of use;

2. Lack of therapeutic efficacy;

3. Risk benefit balance is not positive under the normal conditions of use;

4. Qualitative and quantitative composition is not as declared;

5. Particulars supporting application are incorrect or have not been amended in accordance with Article 23 of Directive 2001/83/EC (vary due to new information).

The following actions (sanctions) are possible (Articles 116, 117 of Directive 2001/83/EC):

- Suspension, revocation, withdrawal or variation of the marketing authorisation;
- Prohibition of the supply of the products or withdrawal from market.

For decentrally authorised products in the case that the CHMP is involved (either on request of a NCA or according to the legal obligation (see 4.4.1) and for centrally authorised products the required measures are determined by the European Commission based on the opinion of the CHMP (Article 107 para. 2 subparas. 3 and 4 of Directive 2001/83/EC, Article 20 para. 2 of Regulation (EC) No 726/2004).

Procedures to vary the marketing authorisation are laid down in Commission Regulation (EC) No 1084/2003 concerning products granted by a NCA and in Regulation (EC) No 1085/2003 concerning products falling within the scope of Regulation (EC) No 726/2004.

3.1.4.5.2 Urgent action to protect public health

Directive 2001/83/EC and Regulation (EC) No 726/2004 allow provisional measures of urgent regulatory actions to protect public health (Article 107 para. 2 of Directive 2001/20/EC and Article 20 para. 4 of Regulation (EC) No 726/2004) with rules of communication and specification of the procedure (referral).

Further actions of the authorities can be

- to conduct pharmacovigilance inspections at the MAH or a substitute (see below);
- to impose penalties (Article 104 para. 9 subpara. 3 of Directive 2001/83/EC, Articles 24 para. 5, 84 para. 1 of Regulation (EC) No 726/2004);
- to change the prescriptions status of a product in case of new facts (acc. to Article 74 of Directive 2001/83/EC).

3.1.4.5.3 Action by the MAH

In case of safety issues the MAH may apply for modification of an existing authorisation (acc. to Regulations (EC) No 1084/2003 and 1085/2003) during the next routine variation, non urgently or within the scope of an urgent safety restriction. In addition, the MAH may withdraw the product.

3.1.4.6 Communication / transparency with stakeholders

3.1.4.6.1 Communication obligations

- The MAH is obliged to timely inform the Competent Authorities in case of new information about the product, which result in changes of the authorisation documents, changes of pharmacological and toxicological documents and changes of SPC (Article 16 para. 2 of Regulation (EC) No 726/2004).
- The MS are obliged to inform the public in case of urgent actions taken to protect public health (Article 20 para. 5 of Regulation (EC) No 726/2004).
- The EMEA is authorised to request at any time data by the MAH, which document that the benefit-risk-ratio remains positive (Article 16 para. 2 of Regulation (EC) No 726/2004).
- The EMEA is obliged to disseminate pharmacovigilance information (Article 57 para. 1 (f) of Regulation (EC) No 726/2004).

3.1.4.6.2 Transparency of communication

The following measures aim to ensure a transparent communication between the involved stakeholders:

Obligation of the MAH:

- The MAH should inform in a timely manner the Competent Authority in case of publication of information regarding pharmacovigilance (Article 104 para. 9 of Directive 2001/93/EC, Article 24 para. 5 of Regulation (EC) No 726/2004).
- The MAH is obliged to provide the Competent Authorities with information regarding his products, especially when these data can result in a change of the benefit-risk-assessment (Article 23 of Directive 2001/83/EC, Article 16 para. 2 of Regulation (EC) No726/2004).
- MAH has to provide upon request of the Authorities data relating to the volume of sales and the volume of prescriptions (Article 23 a of Directive 2001/83/EC).

Access of the public to pharmacovigilance relevant data:

- EudraVigilance database has to be made accessible to the public (Article 102 of Directive 2001/83/EC).
- Pharmacovigilance relevant opinions of the CHMP have to be made accessible to the public (Article 22 of Regulation (EC) No 726/2004).
- Decisions about granting or revocation of a marketing authorisation have to be made accessible to the public (Article 125 of Directive 2001/83/EC).
- Internal procedures, agenda and minutes of the Competent Authorities of the Member States have to be made accessible to the public (Article 126 of Directive 2001/83/EC
- Annually a list with withdrawn medicinal products is published by the European Commission (Article 123 para. 4 of Directive 2001/83/EC).

3.1.4.7 Audit, both of the outcomes of actions taken and of the key processes involved

3.1.4.7.1 MAH – Pharmacovigilance inspections by the authorities

To ensure that MAH comply with pharmacovigilance regulatory obligations Member States' Authorities or the Commission can conduct or initiate pharmacovigilance inspections at random and systematic as well as targeted to MAHs suspected of being non-compliant; various options for actions (as a result of the inspection) can follow and will be judged on a case-by-case basis reaching from education to prosecution (EMEA 2001). The legal basis is laid down in Article 111 of Directive 2001/83/EC and Article 19 of Regulation (EC) No 726/2004.

The legislation appoints as main subjects of the inspections of the pharmacovigilance system the qualified person and reporting (Article 111 of Directive 2001/83/EC).

3.1.5 Conclusions

The basis of the project „Assessment of the European Community System of Pharmacovigilance" is the description of the rules according to which pharmacovigilance of medicinal products is currently performed in the EU.

The legal framework of pharmacovigilance in the EU is essentially formed by

1. Regulation (EC) No 726/2004, appropriate for centrally authorised medicinal products,
2. Directive 2001/83/EC, appropriate for medicinal products that are authorised in more than one Member State through the "Mutual Recognition Procedure" or the "Decentralised Procedure"
3. the national pharmaceutical legislation of the Member States.

Additional laws are Regulation (EC) No 1084/2003 (change of the marketing authorisation of products authorised with the procedure of mutual recognition), Regulation (EC) No 1085/03 (change of the marketing authorisation of centrally authorised products), and Regulation (EC) No 540/95 (non serious adverse drug reactions of centrally authorised products). The legal framework is completed by the guidance document Volume 9 that is associated to the European law and references itself to internationally accepted standards of the ICH Guidelines (ICH-E2A, E2B, E2C, E2D, E2E, M1, M2).

These laws regulate the essential processes of pharmacovigilance such as data collection and data management, safety signal detection, safety issue assessment, decision making, action taken to protect public health and communication with stakeholders.

The analysis above has shown that the current European Pharmacovigilance System has achieved an advanced state of development. This is especially true after the implementation of the recent reform. From November 2005 onwards, Authorities are given additional tools for monitoring the safety of medicines, as well as greater scope for urgent regulatory action once the benefit/risk balance of a medicinal product becomes unfavourable. The new provisions also include increased

transparency on safety issues and facilitate communication, with the provision of timely and targeted information to Healthcare Professionals and the public[7].

This reform is partly inspired by a worldwide discussion of several expert groups who have identified the need to strengthen pharmacovigilance systems especially in the aftermath of the Cerivastatin redrawal. There are current initiatives by the Council for International Organizations of Medical Sciences (CIOMS) and the International Conference on Harmonisation (ICH). The main emphasis of both concepts is to continuously monitor the benefit-risk-profile of a medicinal product as it goes through its life cycle. Their objective is to change the philosophy towards an earlier and more proactive approach that will start before a medicine reaches the market. This leads to a broader concept of pharmacovigilance towards risk management. In parallel with these activities the regulatory agencies in the US and the EU are concentrating their efforts in formulating risk management strategies (Tsintis 2004). More recently, the CIOMS Working Group stressed the need not only to incorporate newer approaches for managing of safety information from clinical trials, but also to adapt the methods and tools used in post-approval pharmacovigilance to the early and late stages of pre-approval development of medicinal products (CIOMS 2005).

As regards the concept of a European Risk Management Strategy (ERMS) two comprehensive key documents were published in spring 2005 as a result of a collaboration between the Heads of the National Medicines Agencies and the EMEA (Heads of Medicines Agencies 2005b). When considering such a strategy, the special interests of patients as regards pharmacovigilance must not be neglected at any rate. This, at least, is one of the core messages of the EMEA/CPMP Working Group with Patients Organisations (EMEA 2004a).

Basis for a further optimisation of the Community system of pharmacovigilance is, however, not only the strengthening of the existing legislation with respect to the implementation of an ERMS but also the full implementation of all legal rules and guidelines in all Member States. Resulting from the complex legal structures of the EU, local deviations from the rules and guidelines in the practical implementation of pharmacovigilance in the Member States have to be assumed due to national conditions and due to the necessary implementation of European Directives into national law.

By analysing potential deviations of the given rules and guidelines, it is to be checked, if the taking into account of local peculiarities, apart from the full implementation of all legal rules and guidelines in the Member States, might further strengthen the Community system of pharmacovigilance.

Beyond this the system may be further optimised, if all involved European stakeholders use the existing instruments for coordination and cooperation and in particular openly and promptly communicate in consideration of the legal obligations.

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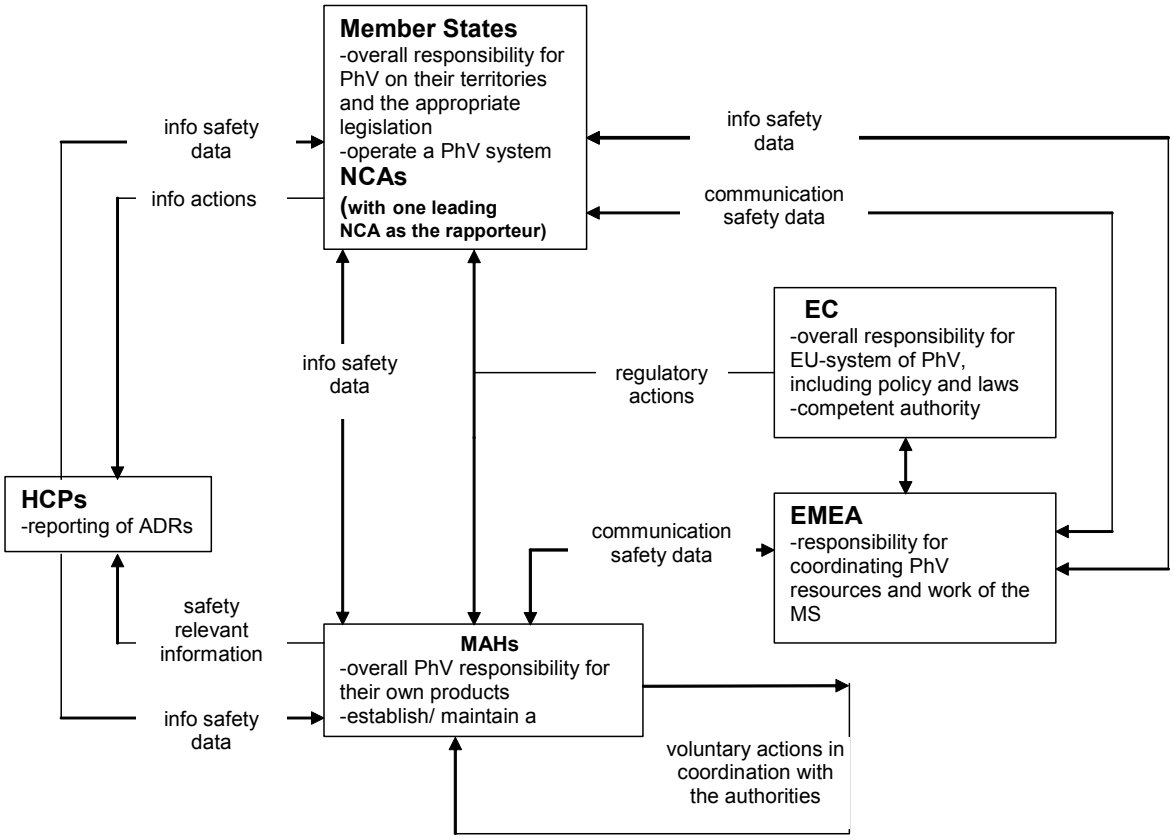
[7] The written agency survey revealed that 60% of the agencies believe that the new legislation will generally improve the system, 2 agencies even believe in a strong improvement.

3.2 Implementation of the European regulatory framework into practice

The functioning of the European system of pharmacovigilance for CAPs is illustrated in the following figure.

Figure 3.18. Organisation of pharmacovigilance regarding centrally authorised medicinal products



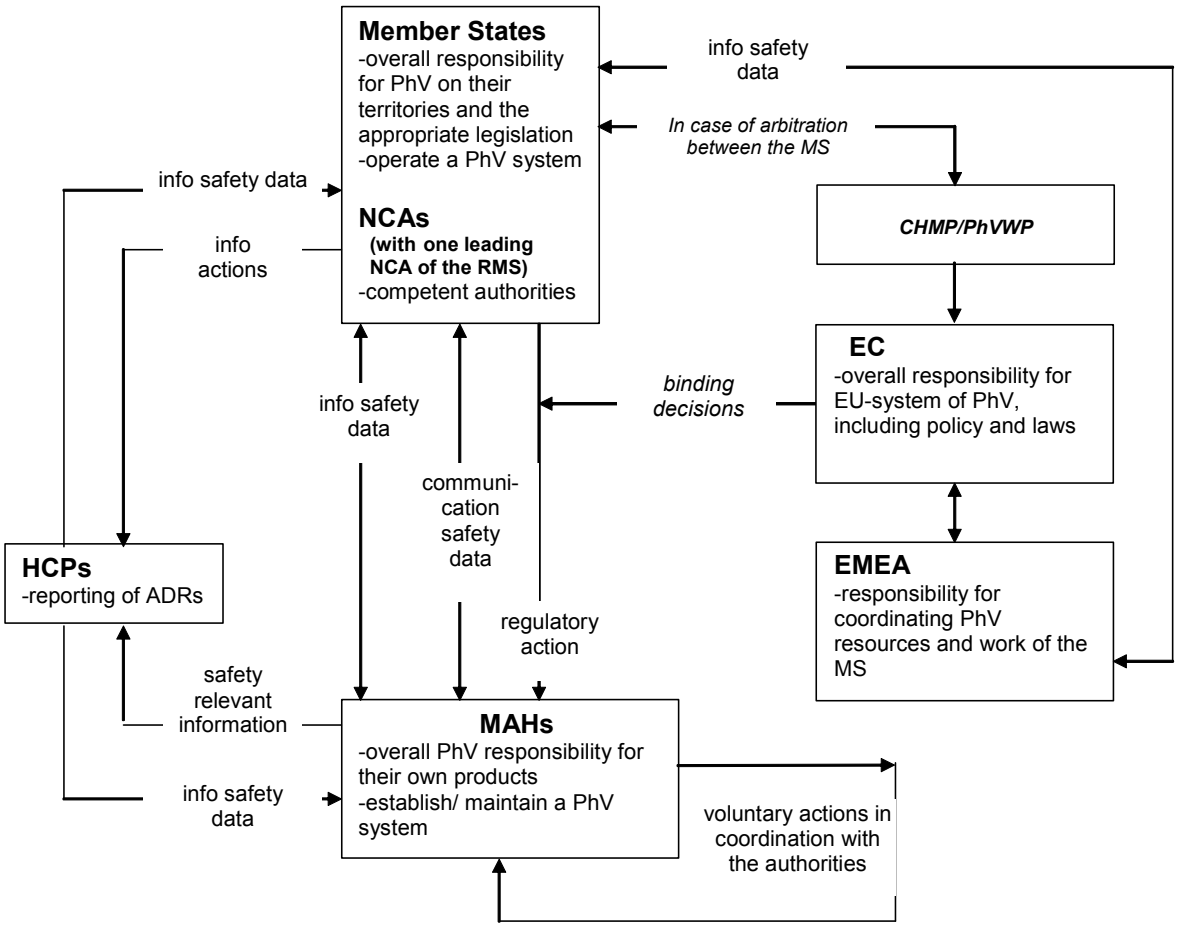
Source: KKS-UKT/Fraunhofer ISI 2005

Figure 3.19 illustrates the main actors and relationships in pharmacovigilance for non-centrally authorised human drugs.

The agency survey revealed that the new requirements that are binding from November 2005 on are not yet implemented in 14 agencies. Most of the agencies plan to implement the new legislation in time; two anticipate delays until 01-JAN-2006 and 01-JUN-2006, respectively.

60% of the agencies believe that the new legislation will generally improve the system, 2 agencies even believe in a strong improvement.

Figure 3.19. Organisation of pharmacovigilance regarding non-centrally authorised medicinal products



Source: KKS-UKT/Fraunhofer ISI 2005

3.3 Systems of pharmacovigilance in other countries

3.3.1 Pharmacovigilance systems in the USA, Japan, and Canada

3.3.1.1 USA

3.3.1.1.1 Legal framework

The Keauver-Harris Amendments ('1962 Amendments') to the Federal Food, Drugs and Cosmetics Acts of 1938 provides the legal basis for drug regulation including the regulations for pharmacovigilance. The amendments do not mandate post-marketing surveillance, but they empower the Food and Drug Administration (FDA) to approve a New Drug Application (NDA) under the condition to conduct post-marketing clinical studies to demonstrate further a product's safety (Arnold 2004).

Safety reporting requirements that oblige a manufacturer to report suspected Adverse Drug Reactions (ADR) to the FDA for all products sold or developed in the

USA are specified in Title 21 of the Code of Federal Regulations (CFR) (Arnold 2004).

The USA, represented by the FDA, are a participant of the International Conference on Harmonisation of Technical Requirements (ICH), so the regulatory agency has adopted almost invariably all ICH-Guidelines which are developed since 1991 (Abraham J. 2004).

3.3.1.1.2 Actors

Main actors of pharmacovigilance in the USA are the government drug regulatory agency, the manufacturer/industry, healthcare professionals (HCPs) and consumers.

The FDA is the US drug regulatory authority. Two departments of the FDA, the Center for Drug Evaluation and Research (CDER) and the Center for Biological Evaluations and Research (CBER) are responsible for assuring the safety and efficacy of all drugs developed or marketed in the USA.

The FDA Office of Drug Safety is responsible for post-marketing ADR reporting of non-biological products and operates the Adverse Event Reporting System (AERS) database for post-marketing pharmacovigilance (Arnold 2004).

The FDA has installed a strong advisory committee system that complements the Agency's scientific expertise. The committees give advice, the FDA is not bounded to follow it. The advisory committees give credibility to the FDA decision-making processes by having public discussion of controversial topics by experts, agency's staff, industry and consumers (Sherman L.A. 2004).

US industry is obliged to establish and maintain records, to report to the FDA all serious, unexpected Adverse Drug Experience (ADE) associated with the use of their products, and to develop written procedures for the surveillance, receipt, evaluation and reporting of post-marketing ADE (Title 21 of the Code of Federal Regulation 310.305 - Records and reports concerning adverse drug experiences on marketed prescription drugs for human use without approved new drug applications. Revised as of April 1, 2004 2004, Title 21 of the Code of Federal Regulation 314.80 – Post-marketing reporting of adverse drug experiences 2004).

3.3.1.1.3 Post-marketing surveillance activities

Spontaneous reporting system

Database: The FDA operates the Adverse Event Reporting System (AERS) computerized database since 1969 and the Vaccine Adverse Event Reporting System (VAERS). In 2004 the AERS database had stored 3 million reports (Goetsch R. 2005).

Used definitions: Definitions are laid down in the 21 CFR and are in general consistent with the corresponding ICH definition. The term ADE is used within the USA rather than Adverse Event (AE) or ADR. An ADE is defined as any AE associated with the use of a drug whether or not to be product related. It includes spontaneous reports (Arnold 2004).

Reporting: HCPs and consumers report ADE voluntarily to the FDA (10% of all reports to the FDA; Goetsch R. 2005). They can report electronically using the online access of the MedWatch program (MedWatch 2003, MedWatch 2005b). Industry is legally obliged to report ADEs (MedWatch 2005a), which make more

than 90% of all reports (Goetsch R. 2005). They can submit ADR electronically (MedWatch 2005a).

Public access: The AERS collects information about adverse events, medication errors and product problems that occur after the administration of approved drug and therapeutic biologic products. Quarterly (non cumulative) data files since January 2004 are online available (AERS 2005a).

Figure 3.20. Expedited reporting requirements in the USA

Report	Origin	ADR that qualify for expedited reporting to the regulators
• 15 day alert report • 15 day alert report follow-up (if the initial report is incomplete)	• Regardless of the source (domestic cases, foreign cases, scientific literature	• Serious and unexpected ADE
• 15 day alert report • 15 day alert report follow-up (if the initial report is incomplete)	• Study reports, solicited information	• Serious and unexpected ADR (reasonable possibility of a causal relationship), if minimum criteria acc. to ICH E2A are obtainable.

Source: Arnold 2004, Title 21 of the Code of Federal Regulation 310.305 - Records and reports concerning adverse drug experiences on marketed prescription drugs for human use without approved new drug applications. Revised as of April 1, 2004 2004, Title 21 of the Code of Federal Regulation 314.80 – Post-marketing reporting of adverse drug experiences 2004

Periodic safety reporting by industry

The periodic reports should contain the reporting form (ADE, ADR) and a line listing of the spontaneous reports, narrative summaries and analysis and narrative discussion of actions. FDA accepts periodic reports in accordance with ICH E2C format and content, if the applicant has secured a waiver from the FDA (Arnold 2004).

Periodicity (Title 21 of the Code of Federal Regulation 314.80 – Post-marketing reporting of adverse drug experiences 2004): Submission is required quarterly during the first 3 years after marketing approval, thereafter annually.

Figure 3.21. Reports qualifying for inclusion in a US periodic report

Source	Type of reports qualifying for inclusion in a periodic report
• Spontaneous reports	• All domestic ADEs (serious expected, non-serious) • Foreign serious unexpected ADEs • Domestic reports of "lack of efficacy"
• Published literature	• Only serious unexpected ADEs
• Clinical studies and post-marketing studies	• Only serious unexpected ADRs

Source: Arnold 2004

Conditional approval

FDA can approve a NDA under the condition to conduct post-marketing clinical studies to demonstrate further the product's safety (Title 21 of the Code of Federal Regulation: 310.303 - Continuation of long-term studies, records, and reports on certain drugs for which new drug applications have been approved 2004).

Post-marketing study commitments

Post-marketing study commitments are studies, required of or agreed to by a sponsor, that are conducted after the FDA has approved a product for marketing. Agreement with the sponsor to conduct a study can be reached either before or after FDA has granted approval to a sponsor to market a product. The studies are used to gain new data about the safety, efficacy or optimal use of a drug. The sponsor is obliged to provide an annual report to the FDA on the status of the study until it is completed or terminated. The FDA is responsible to annually report in the Federal Register on the performance of post-marketing commitment studies (AERS 2005b).

3.3.1.2 Japan

3.3.1.2.1 Legal framework

The primary Japanese law governing drug affairs is the Pharmaceutical Affairs Law (PAL) which is the legal basis of pharmacovigilance requirements. The PAL is supplemented by the following post-marketing provisions issued by the Ministry of Health, Labour and Welfare (MHLW; Arnold 2004):

- Standard for implementation of post-marketing surveillance (PMS) for the re-examination application of new drugs (1993);
- Standard for the conduct of Good Post-Marketing Surveillance Practice (GPMSP) (1993) and MHLW Ordinance No.10 (GPMSP) (1997);

- Ordinance No.29 – Enforcement of the Pharmaceutical Affairs law, Article 66-7 (1997);
- Notification No. 1324 – Implementation of early post-marketing phase vigilance (2001);
- Notification IYACUAN No. 0531001 – Electronic reporting (2002).

Japan, represented by the government drug regulatory agency, is a participant of the ICH, so the regulatory agency has adopted almost invariably all ICH-Guidelines which are developed since 1991 (Abraham J. 2004).

3.3.1.2.2 Actors

Main actors are the government drug regulatory agency, the industry, HCPs and consumers.

Since April 2004 the Pharmaceutical and Medical Device Agency (PMDA) with a safety division is regulatory responsible for the handling of affairs concerning safety. An independent expert advisory committee exists which is targeted to review reports of reactions that may warrant labelling changes (McEwen J. 2004).

To fulfil the requirements for post-marketing surveillance Japanese companies establish a PMS Management Department with sufficient qualified staff that is independent from the sales/marketing department. They must appoint a “Responsible Person” for PMS management and they have to prepare and to comply with relevant standard operating procedures (Arnold 2004).

3.3.1.2.3 Post-marketing surveillance activities

1. Spontaneous reporting system:

Used definitions: Japanese definitions are in general in accordance with those specified in the ICH guidelines. MHLW excluded the “medically important” criterion from the definition of a serious AE and slightly changed “disability” to “any disablement that is a permanent dysfunction that causes a disturbance in daily life” (Arnold 2004).

Reporting: Main source of adverse drug reactions’ report is the industry that is obliged to report occurred serious ADR. In the year 2002, 24221 ADR reports were transmitted by the industry, and 4195 ADR reports by Healthcare professionals (HCPs). There is no consumer reporting (McEwen J. 2004).

Electronic reporting is mandatory for industry for expedited reports since October 2003, electronic reporting is not available for HCPs (Arnold 2004, McEwen J. 2004).

Public access: Japanese ADR reports are available on the internet and can be accessed by researchers outside the national centre (Kubota and Koide 2004).

Figure 3.22. Expedited reporting requirements in Japan

Report	Origin	ADR that qualify for expedited reporting
• 15 day	• Domestic	• Serious and unexpected (Fatal unexpected ADR: immediate notification to be followed by full written report
	• Foreign	• Serious and unexpected
	• Scientific literature	• Serious
• 30-day	• Domestic	• Serious and expected
		• Severe/moderate non-serious
		• ADRs with an increased frequency, lack of efficacy, possibility of an association with the onset of cancer
Expedited	Abroad	• Measures taken abroad that relate to safety issues

Source: Arnold 2004

Periodic safety reporting by the industry

The Periodic Safety Update Report (PSUR) is to be submitted for all drugs marketed in Japan prepared in full accordance to the ICH E2C guideline, including foreign data. The PSUR must summarise the progress of all Japanese post-marketing studies (Arnold 2004).

The PSURs have to be submitted every 6 months for 2 years following approval of the Japanese NDA, then annually during the defined re-examination period, and finally every 5 years after the re-examination period is finished (Arnold 2004).

Drug Re-examination System

To overcome the known limiting factors of pre-approval clinical studies (limited number of involved patient, a selected population) Japan has instituted in 1979 the Drug-Re-examination System for reassessing the safety and efficacy of a drug after its first approval. During the re-examination time the initial approval is only provisional and must be reviewed subsequently considering the efficacy and safety of the product at a specified future time point that depends upon the nature of the drug (after 4 years for supplemental NDA, 6 years for most drugs, when they are approved for the first time in Japan, and 10 years for orphan drugs). Practically efficacy and safety of a drug are scrutinised by comparing the data collected during post-marketing surveillance activities with the data submitted at the time of approval of the drug. The outcome of the second review can be the cancellation or modification of the initial approval or no action (Fujiwara and Kobayashi 2002, Arnold 2004).

Post-marketing surveillance activities (Arnold 2004)

- Early Post-marketing Phase Vigilance
    - during the first 6 months after entry of a new product to the Japanese market;
    - ensures that information has been provided to the prescribers and encouragement of caution;
    - improvement of appropriate use;
    - reporting promptly spontaneous information on serious ADRs, to implement consequent safety measurements and minimize risk for the public health;
- Clinical Experience Investigation studies
    - Detection of unlabelled ADRs;
    - Understanding of ADR development during actual use;
    - Definition of factors suspected to influence the product's safety and/or efficacy profile;
- Special studies and post-marketing clinical studies
    - E.g. long-term use, special populations, pharmacoepidemiological studies with mortality outcome, pharmacokinetic studies with patients with renal failure.

3.3.1.3 Canada

3.3.1.3.1 Legal Framework

Basic Law

In Canada legislative requirements for the post–marketing surveillance of health products are covered by the Food and Drugs Act and Regulations (Health Canada 2005a).

Canada is not a participant of the ICH, but one of its non-voting observers. Some of the ICH-guidelines are adopted (Abraham J. 2004).

3.3.1.3.2 Actors

Main actors are the government drug regulatory agency, the industry, HCPs and consumers.

The Marketed Health Product Directorate (MHPD) of Health Canada (the Canadian Federal Department) is the regulatory office that is responsible for post-marketing

safety, concerning all regulated marketed health products in Canada (MHPD 2005).

There are established a number of expert advisory committees and public advisory committees to increase transparency and public involvement (Health Canada 2005d).

3.3.1.3.3 Post-marketing surveillance activities

Spontaneous reporting system

Database: Health Canada operates the Canadian Adverse Drug Reaction Information System (CADRIS). January 2004 CADRIS contains over 160000 suspected ADR reports that have occurred in Canada since 1965 (Health Canada 2005c).

Used definitions: The definitions for adverse reactions harmonize with the definitions of the World Health Organisation, Council for International Organizations of Medical Sciences (CIOMS), ICH and FDA (Health Canada 2003).

Reporting: ADR reporting applies to all drug products sold in Canada.

HCPs and consumers report voluntarily adverse drug reaction, at the moment to 7 regional ADR centres and 1 national ADR centre or to the manufacturer. Electronic reporting will be possible in fall 2005 (Health Canada 2005b).

Manufacturers are legally obliged to report adverse drug reaction to the regulatory authority (Health Canada 2003).

Public access: The Canadian Adverse Drug Reaction Monitoring Program (CADRMP) Online Query and Data Extract utility provides the public with information about suspected adverse reactions of marketed products occurring in Canada (Health Canada 2004a).

Figure 3.23. Expedited reporting requirements in Canada

Report	Origin	ADR that qualify for expedited reporting
• 15 days	• Domestic cases • Including literature	• Serious • Lack of efficacy (only new drugs)
	• Foreign cases • Including literature	• Serious and unexpected
	• Domestic study reports	• Serious • Lack of efficacy (only new drugs)
	• Foreign study reports	• Serious and unexpected

Source: Health Canada 2003

Periodic reports by the industry

On an annual basis and whenever requested the manufacturer is obliged to prepare a summary report about the reports received during the last twelve months. The summary consists of three sections: a summary line listing of ADRs, a critical analysis of the reports and recommended actions (Health Canada 2003).

Figure 3.24. Reports qualifying for inclusion in a Canadian summary report

Source	Type of reports qualifying for inclusion in a periodic report
• Spontaneous reports and literature	• Domestic ADRs (serious, non-serious and unexpected, lack of efficacy of new drugs) • Foreign ADRs (serious, non-serious)
• Studies	• Domestic ADR (serious and unexpected, lack of efficacy of new drugs) • Foreign ADR (serious and unexpected)

Source: Health Canada 2003

Additional post-marketing surveillance activities (Health Canada 2004b)

- Post-marketing studies conducted by the manufacturer or health care institutions
- Publications in scientific journals
- Collaboration with patient group, academic institutions, professional associations in Canada and internationally
- Risk communication from regulatory agencies in other countries

3.3.1.4 Summary

The comparison of the pharmacovigilance systems in the USA, Japan and Canada has pointed out that the organisation of this surveillance is basically the same in these three countries.

Main actors involved are the national drug regulatory authorities, the manufacturers of the drugs and the HCPs. The legal requirements to collect information about adverse drug reactions are implemented using spontaneous reporting systems (provided primarily with reports by manufacturers and the HCPs) and periodic reports of marketed drugs (prepared by the manufacturers of the products).

The authorities in all 3 countries operate databases for the collection of spontaneously reported adverse drug reactions. Each of these databases is accessible for the public to retrieve information about a certain drug. In all countries the authorities can get advice from expert advisory committees. Two countries, the USA and Japan, are participants in the ICH; Canada is a observer of the group. As a result

the basic conditions of pharmacovigilance are harmonised within the three countries and with regard to other members of the ICH.

Concerning the access of drugs to the market, however, the FDA can approve drugs under the condition to conduct post-marketing studies in order to demonstrate further a product's safety, while in Japan the re-examination system gives the possibility to reassess the safety and efficacy of a drug after its primary provisional approval at a specified time point depending upon the nature of the drug.

In the USA and Canada the public is integrated in the discussion about safety issues through participation in public meetings of advisory committees (USA) or the membership in a public advisory committee (Canada). Consumers are invited to report adverse drug reactions directly to the authorities; in the USA this can already be done electronically. The frequency to prepare periodic safety reports differs between the three countries. In the USA, the reports have to be submitted quarterly in the first three years following the approval; in Japan this has to be done every 6 months for 2 years following approval of a Japanese NDA and then annually during defined re-examination period; in Canada reports are required to be prepared annually or on request.

The comparison of the pharmacovigilance related activities in the USA, Japan and Canada with the European system shows that definitions and processes accord to some extent. On the other hand it seems worthwhile to explore in more detail the specific conditions in the USA, Japan and Canada, e.g. the conditional approval or publicly accessible ADR-databases, in order to be able to asses whether and how such provisions could contribute to strengthening the European system.

3.3.2 Evaluation of foreign systems by interview partners

In the following we present the most frequent answers on the interview question (number 11), "What could we learn from other systems in 3rd countries?" In general, the interviewees here referred to non-European countries, most frequently the systems in Australia and New Zealand were mentioned as having particular strengths. If statements were made about European countries they are presented in chapter 8.2, together with other examples of best practice from the interviews.

3.3.2.1 General factors

Legal framework conditions

One of the interviewees from agencies assessed the regulation in USA and Japan as less requiring than in Europe.

Expertise

Australia and New Zealand were said to have particularly efficient ADR advisory boards (with clear responsibilities, detailed preparation by the authority, exchange with MA department, concentration on "drugs of current interest" with intensive monitoring programmes and prescription event monitoring especially for new classes of drugs.

The FDA has well developed expertise in pharmacoepidemiology internally. The good information and respective courses in epidemiology and individual training offered by the WHO-UMC were equally appreciated. The training is free of charge.

In Canada the competent authority (HealthCanada) is effective because it has all products in one hand (medicines, dietary supplements…). Australia is said to have good information on the market.

3.3.2.2 Data collection

The intensive monitoring programme/ drugs of current interest/Prescription event monitoring of Australia and New Zealand are mentioned as good practice by several interviewees. To detect signals, several interviewees find that the practice of the UMC to use all reports, and not only reports on severe ADRs, is helpful. The Australian system is said to offer good information on the market. Single interviewees found that the system in the USA is strong because of the large amount of data, but weak because of its low data quality. Another interviewee gave an interesting example from Taiwan where HCPs at a certain time got presents for reporting which led to over-reporting and equally reduced quality of safety data.

Australia, New Zealand, and Canada have strengths in product-related PASSs.

3.3.2.3 Safety issue assessment

Co-operation

One interviewee from an agency requested that the WHO ADR monitoring programme used in 3rd countries should be harmonized with the European system to improve the opportunity of co-operation.

Access to external experts

Several interviewees emphasized the good work of the ADR advisory boards in the Australian system.

3.3.2.4 Decision-making

According to a single opinion, the system in the USA comes to relatively quick decisions.

3.3.2.5 Communication and action to protect public health

In general, much good information is seen by the interviewed agencies coming from Australia, New Zealand, Canada, and the WHO. Several interviewees praised the good quality of information on the websites of the Canadian and US agencies.

More publications of changes e.g. in SPCs than in Europe are identified by a number of interviewees in the USA and in Australia, in the latter country the quality of the ADR bulletin as well as the publication of informative protocols of expert meetings were also mentioned by several interviewees. The USA have as an advantage a high transparency, e.g. by stakeholder discussions with public representation. A good example to communicate ADRs to HCPs is the electronic ePocrates-system that informs HCPs on all aspects of drugs on an electronic formulary and uses this platform to give safety-relevant information too.

HealthCanada offers a good website including safety data that are published for public use in the Canadian Adverse Drug Reaction Monitoring Program (CADRMP) database.

3.4 Other framework conditions

A mean of 5038 products per country had a life national marketing authorisation (NAPs) in 2004, with a range from 236 to 13,678 products. 731.4 products (MRPs) per country (range 34 to 2207 products) had an authorisation under the Mutual Recognition procedure. The number of Centrally Authorised Products (CAPs) is equal for all countries. The figure of 269 CAPs authorised in 2004 was given by EMEA based on data from DG ENTR.

Table 3.1. Number of approvals for NMEs per country in 2003 and 2004

Number of approvals for NMEs per country			
2003	**Minimum**	**Maximum**	**Median**
National approvals	0	42.00	1.00
MR procedure	0	68.00	5.50
MR with country as RMS	0	6.00	.00
Centralised with country as rapporteur	0	21.00	.50
2004	**Minimum**	**Maximum**	**Median**
National approvals	0	45.00	.00
MR procedure	0	75.00	3.00
MR with country as RMS	0	14.00	.00
Centralised with country as rapporteur	0	36.00	1.00

Source: Fraunhofer ISI 2005

Table 3.2 compares the values of the own survey with those collected in the ERMS Surveys of 2002 and 2004.

Table 3.2. Time acting for the Community as Rapporteur

	Old MS in 2002 ERMS [%]	**New MS in ERMS 2004 [%]**	**Own survey data for 2004 [%]**
Minimum	0.00	0.00	0.00
Maximum	35.00	0.00	38.00

Source: Fraunhofer ISI 2005

The share of work that is done by the agencies for the Community as Rapporteur varies significantly. The same is true for the time that is spent for the Community as Reference Member State (RMS) for a MRP (Table 3.3).

Table 3.3. Time acting for the Community as RMS

	Old MS in 2002 [%]	New MS in 2004 [%]	Own survey data for 2004 [%]
Minimum	20.00	0.00	0.00
Maximum	99.00	100.00	99.00

Source: Fraunhofer ISI 2005

Most of the time, however, is spent in most agencies on NAPs. Exceptions are Cyprus, Liechtenstein, Hungary, Latvia, the Netherlands, Denmark, Sweden, Ireland, Finland, Malta, and the UK, who spend a maximum of 30% of their work on NAPs.

The number or physicians working in a country will also influence the reporting of ADRs.

Table 3.4. Number of physicians

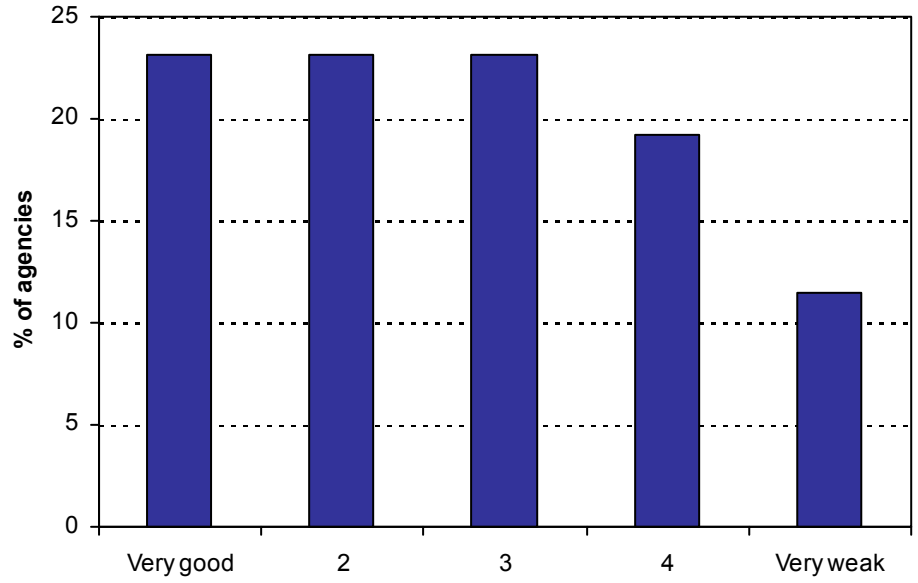
	Physicians outside hospitals	Physicians in hospitals	Physicians total
AT	17845	17443	35288
BE	,	,	45991
CZ	17000	16000	33000
DE-BFARM	133000	146000	279000
DE-PEI	160078	146357	306435
DK	4600	8600	13200
EE	800	,	,
EEA-28	1583000	,	,
EI	,	,	7500
ES	,	,	179033
FI	11000	7000	18000
FR	110000	64700	174700
HU	24560	14317	38877
IC	1290	660	1950
IT	310000	50000	360000
LI	55	10	65
LT	6640	6757	7258
LU	1200	,	,
MT	,	,	1302
NL	9849	20060	29909
NO	5000	10000	15000
PL	89000	,	,
PT	7251	20733	27984
SE	12000	18000	30000
UK[8]	41340	98000	139340
DE-total	160078	146000	,

Source: Fraunhofer ISI 2005; figures given by the Agencies.

The political support for pharmacovigilance in general was assessed by the agencies. The results are presented in Figure 3.25.

8 Figures are for Great Britain only, i.e. data exclude Northern Ireland.

Figure 3.25. Political support for PhV



Source: Fraunhofer ISI 2005

The support is assessed as very good or good (values 1 or 2) only by half of the agencies, and as weak or very weak (values 4 or 5) by nearly one third.

The overall compliance of MAHs with the legal requirements is assessed as very good or good by 78% of the agencies, negative or very negative assessments did not occur at all.

3.5 Resources for pharmacovigilance

3.5.1 Budget

The financial resources differ widely between the agencies. The budget per population indicates that these differences are not solely explicable by the size of the countries (Table 3.5).

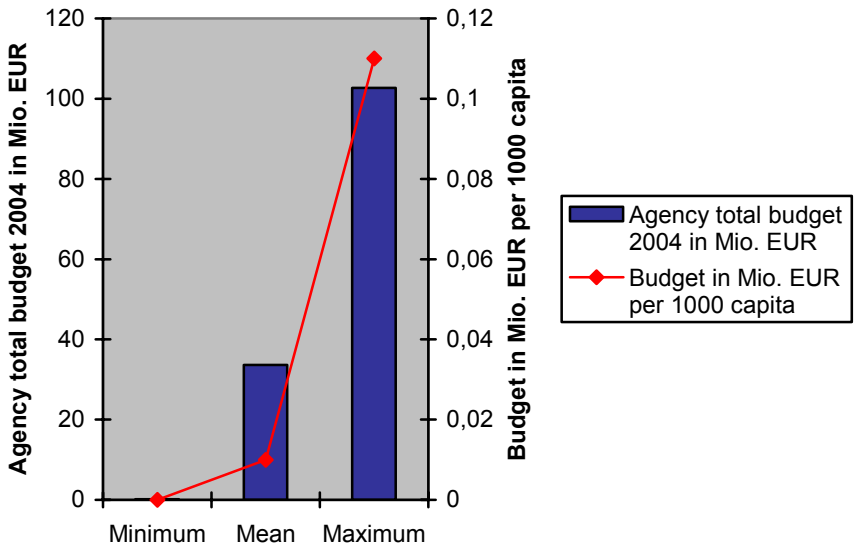
Table 3.5. Agency budget 2004

	Minimum	Maximum	Mean
Agency total budget 2004 in Mio. EUR	0.13	102.67	33.68
Budget in Mio. EUR per 1000 capita	0.00	0.11	0.01

Source: Fraunhofer ISI 2005

The same figures are presented in the following diagram.

Figure 3.26. Average agency budget in 2004



Source: Fraunhofer ISI 2005

The funding of the agencies is quite different. A lot of agencies are totally financed by public funding, some are financed through a mix of public funding and fees (mostly from MAH) and a few agencies are solely financed by fees.

3.5.2 Staff

Only a small part of the agency's resources are directly dedicated to PhV. The median proportion of PhV staff is only 5% of the total agency staff. About two-thirds of the PhV staff is devoted to scientific tasks.

The median number of staff in the national agencies is Md=7.13 FTE over all agencies (small and large countries). The relationship of PhV staff for administrative tasks to scientific staff lies between 0.00 administrators per scientist (that means no administrative staff at all) and 5 administrative staff per scientist, with an average of Md=0.37 administrative staff per scientist.

Table 3.6. PhV staff in national agencies

	Median	Minimum	Maximum
Staff total Agency [FTE]	170.00	1.40	911.00
PhV staff total [FTE]	7.13	0.10	60.00
Share of PhV-staff of total staff	5%	1%	8%[1)]
PhV staff administrative [FTE]	2.50	0.00	41.00
PhV staff scientific [FTE]	4.50	0.10	43.70
Proportion of administrative PhV staff to scientific PhV staff	37%	0%	500%

1) One country with an extreme value of 35% of PhV staff was dropped.

Source: Fraunhofer ISI 2005

As expected there are differences between the countries in size of the staff, but also in the proportion of administrative to scientific staff.

A more detailed analysis of the required staff in the different process stages shows the highest value for "Regulatory action" (Table 3.7).

Table 3.7. PhV staff in different process stages (multiple responses possible)

Staff involved in processes [persons]	
	Median
Data coll./entry	3.00
Data management	2.00
Risk assessment	3.00
Regulatory action	4.00
Risk communication	2.00
Audit and QA	1.00
Monitor. compliance	1.25

Source: Fraunhofer ISI 2005

The combined staff of national agencies and the regional centres can be set in relation to the total population in one country. The highest value was achieved by a small country that collaborates very intensively with a regional centre in a neighbour country, therefore as maximum the second-highest value is given coming from a country that acts independently. The EMEA is also left out of this analysis, having the lowest value of 0.1 FTE per million European (i.e. EEA-28) citizens.

To account for the different size of the countries, the available staff for pharmacovigilance (scientific plus administrative) was divided by the size of the populations (see following table).

Table 3.8. Total national staff for PhV per capita

	PhV-staff NCA [FTE per million capita]	PhV-staff NCA+RC [FTE per million capita]
Minimum	0.2	0.2
Median	0.772	1.183
Maximum	4.6	4.6

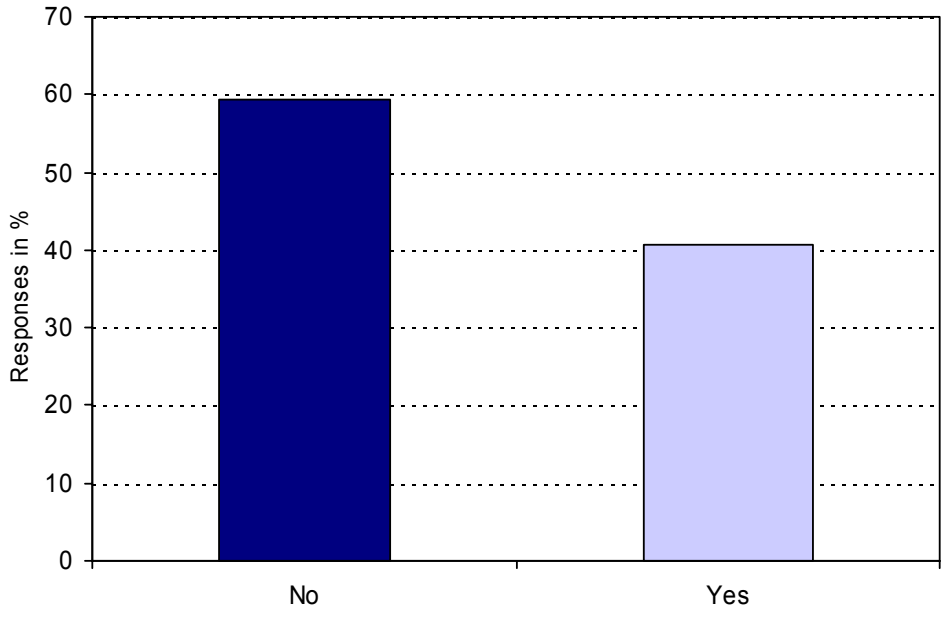
Staff for pharmacovigilance, scientific and administrative.

Source: Fraunhofer ISI 2005

3.5.3 Collaboration in national system

The national agencies of bigger countries have the possibility to collaborate with regional centres for PhV. This is the case in 12 of the answering 29 countries (Figure 3.27).

Figure 3.27. Existence of regional centres



Source: Fraunhofer ISI 2005

The staff for regional centres in these countries differs between 5 and 82 persons. The regional centres are usually specialised in and responsible for some PhV

tasks. They are in all eleven countries with regional centres responsible for data collection, but – as expected – none of them for decision making (Table 3.9).

Table 3.9. Tasks of regional PhV centres

	N of countries
Data coll./management	11.00
Signal detection	7.00
Safety issue assessment	7.00
Decision making	.00
Communication	6.00
Scientific studies	8.00
Informal advice	7.00
Inspection of MAHs	.00

Source: Fraunhofer ISI 2005

In some countries the regional centres are responsible for the total collection of ICSRs, in other countries they play only a minor in this process stage (Table 3.10).

Table 3.10. Number of ICSRs collected by regional PhV centres

		N of regional centres	Total N of reports collected by all regional centres	% of ICSRs collected by regional centres 2004
Country	**DE**	6	1000	6.35
	ES	17	7476	100.00
	FR	31	20116	100.00
	NL	1	5050	100.00
	NO	5	1490	86.00
	PL	3	92	8.86
	PT	3	1104	64.26
	SE	6	4124	100.00
	UK	5	5054	25.21
	LU	1	n.a.	n.a.

Source: Fraunhofer ISI 2005

The median population-based reporting rate is 160 (see Table 3.17). Above this limit lay the 12 countries **SE**, **NO**, DK, **UK**, **FR**, **NL**, BE, **DE**, FI, SL, **ES**, **PT**, and SV, 8 of these 12 (those printed in bold) have regional centres. This is a strong indicator that the RCs contribute to high reporting rates.

In addition to regional centres there are some other possibilities for the national agencies to collaborate in PhV. Most common is contracting-out tasks to academia and to HCPs.

Table 3.11. Contracts with other actors in PhV assessments

Contracting-out to...	
	N of countries
Contract out to academia	15
Contract out to HCPs	13
Contract out consultants	5
Contract out RCs	6

Source: Fraunhofer ISI 2005

3.5.4 Competences

In combination of national agencies with regional centres and external experts, most of the countries have competences in the various fields of PhV (Table 3.12), but for smallest countries it is quite a problem to get enough national expertise at least in some fields.

Table 3.12. Competences available in countries

	National agencies	**Regional centres**	**External Experts**	**Not at all available in country**
Exp.toxicol.	17	1	18	3
Animal studies	15	,	20	2
In vitro testing	16	,	17	3
Pharmacology	21	7	20	1
Medicine	26	10	20	,
Pharmacoepi	17	6	20	1
Epidemiology	13	4	22	1
Statistics agency	17	3	21	1
Human ADRs/veterinary products	13	2	11	4
Design PhV plans	19	1	10	5
Regulatory affairs	27	1	6	,

Source: Fraunhofer ISI 2005

Most of the countries have a special expert committee dedicated to PhV. This is the case for 20 of the answering 28 countries (EU25 + EEA) and an improvement

compared to previous surveys. The countries with no expert committee are mostly small countries.

The expert committees meet in median five times per year. This is a small reduction compared to the previous surveys (Table 3.13).

Table 3.13. Expert committee meetings per year

	Minimum	Maximum	Median
PhV comm. meetings p.a. ERMS 2002	1	30	6
PhV comm. meetings p.a. ERMS 2004	5	11	7
Expert committee meetings (own survey)	0	22	5

Source: Fraunhofer ISI 2005

In 11 countries the expert committee is not only responsible for PhV, but for marketing authorisation and variations (e.g.) as well.

3.5.5 International collaboration

The national agencies contribute in different aspects to the EEA PhV system. 14 of the countries have already been rapporteur for a centrally approved product (CAP). 17 of the 26 countries that answered this question in the survey have also the capability of leading EU-wide co-ordination of regulatory action and communication of drug safety issues. But the most important routine task in internal collaboration is the writing of assessment reports with a median of 25 reports per country and country (Table 3.14). One agency produced 2012 assessment reports. On average, 1.63 assessment reports were written per staff FTE, with a maximum of 231 assessment reports per person. 0.23 Legal documents/guidelines were prepared per staff FTE.

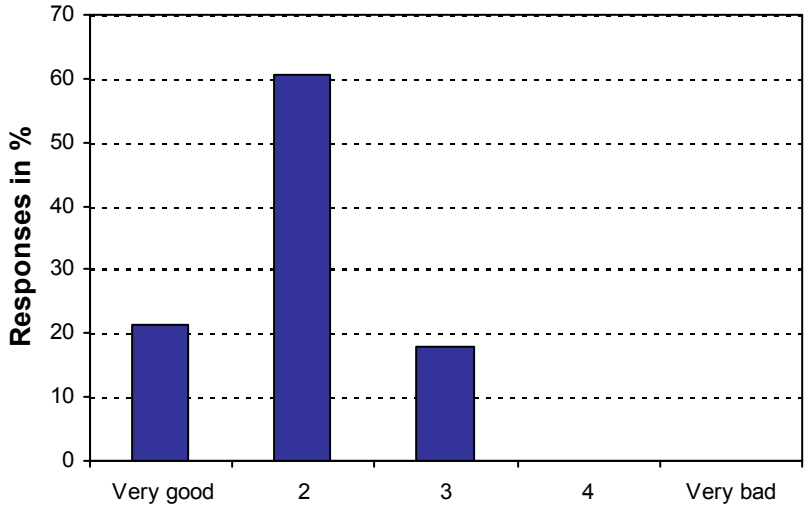
Table 3.14. Contributions to EEA PhV system

	Minimum	Maximum	Median
Assessment reports written	.00	2012.00	25.00
Answers to the CHMP	.00	75.00	.00
Answers to CHMP per staff FTE	.00	6.82	.00
Legal documents/guidelines prepared	.00	131.00	2.00

Source: Fraunhofer ISI 2005

The majority of the national agencies consider their cooperation with the EMEA positive (Figure 3.28).

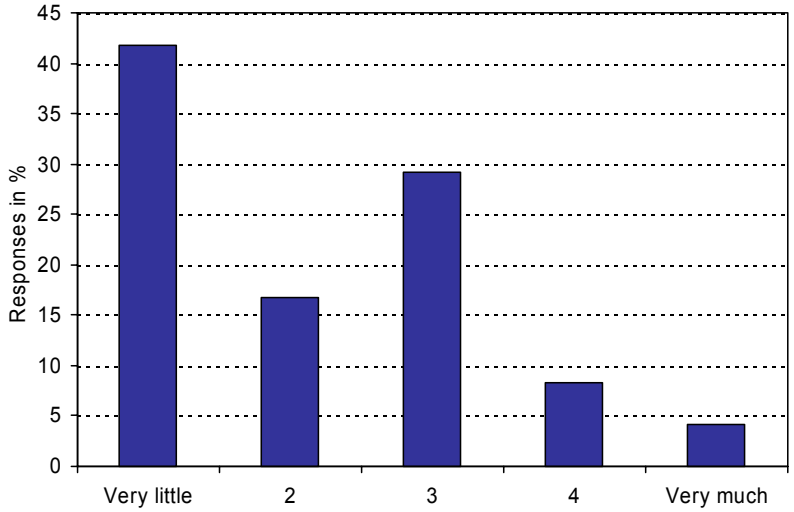
Figure 3.28. Cooperation between national agencies and EMEA



Source: Fraunhofer ISI 2005

One goal in the internal collaboration is the reduction of duplication of work. At the moment the agencies have a quite different opinion about how much work is done in signal detection and safety issue assessment in duplicate within the own country and at the same time in other MS or on EU level. But the majority thinks that the duplication of work is rather little. A more detailed analysis of this issue reveals that more duplication of work is experienced by the larger countries and most of the old MS (potentially these are also the countries that have in the past contributed the most to community tasks), whereas the smaller and new MS assess duplication of work to be very little.

Figure 3.29. Duplication of work

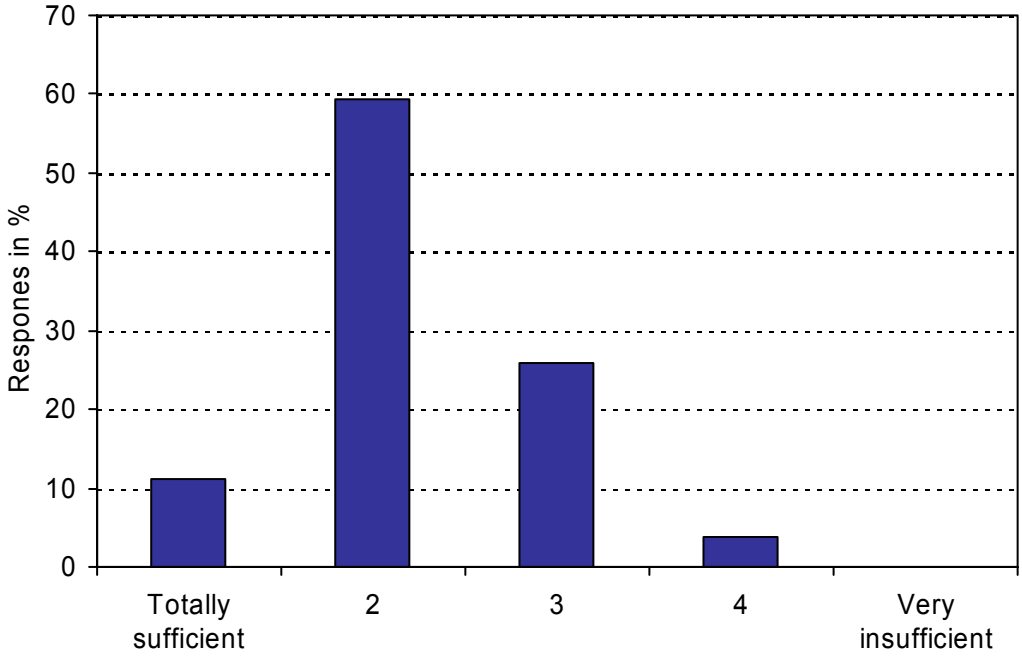


Source: Fraunhofer ISI 2005

3.5.6 Technical resources

In addition to financial and personal resources the technical resources are important for PhV work. As expected, almost the whole staff in all agencies has a PC and evaluates the number of PCs as sufficient. Almost all of the agencies also have a local area network, permanent internet access and IT support. But not in all agencies the IT resources are completely satisfying the needs, as the assessment of the IT-resources in the following figure shows.

Figure 3.30. Assessment of IT-resources



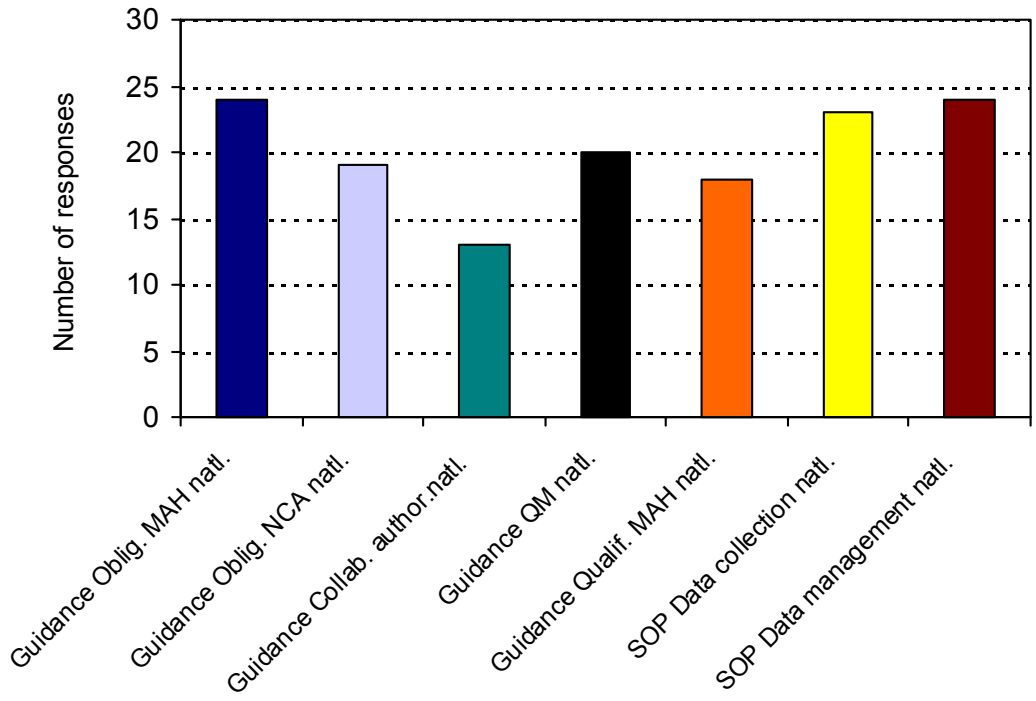
Source: Fraunhofer ISI 2005

3.5.7 Definitions and standards

Guidance documents play an important role for the assurance of standards in PhV. Most of the agencies have own national versions for the relevant guidance and SOPs, as can be seen in (Figure 3.31 and Figure 3.32).

Of all guidance documents, those for obligations of MAHs, data management, data collection, feedback to reporters, and obligations of the NCA are the most common ones. Relatively infrequent are guidances on Collaboration with other authorities and international health institutions, signal detection and decision-making.

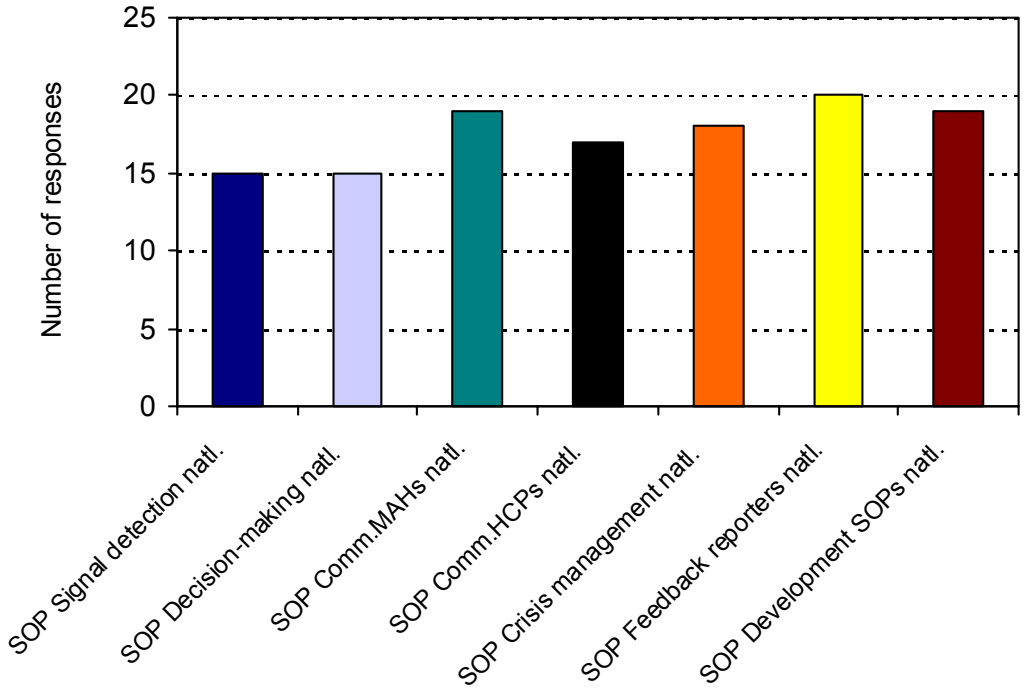
Figure 3.31. Guidance in national version (part 1)



Source: Fraunhofer ISI 2005

The following diagram contains the respective figures for a second set of guidance documents.

Figure 3.32. Guidance in national version (part 2)



Source: Fraunhofer ISI 2005

For the cases where no national document exists, there is usually an EU document available. Only in exceptional cases it is claimed that there exists neither a national nor an EU document.

3.6 General quality management

To assure the quality of their PhV system the national agencies use different possibilities. This depends of course at least in part on their in-house and external resources. A systematic quality management is not implemented in the most PhV departments. In a few countries the PhV department is part of an agency Quality-Management. Some others have either an internal audit or an external peer review.

More common approaches to ensure the quality of the PhV system are the usage of internal or external expertise in certain process stages of PhV. Especially emphasis is set on the collaboration with external experts. This happens in different ways:

- consultation external experts, e.g. for PSUR evaluation
- support of expert committees, especially in the process of decision-making
- usage of external assessment reports and literature

There are also different approaches by using in-house competence to ensure quality:

- usage of relevant SOPs as guidelines (most common)
- analysing of earlier decisions or cases
- regular (daily, weekly) PhV department meetings
- meetings if there are new signals.

Less emphasis in regard to quality assurance is set on the electronic support of signal detection, e.g. statistical calculation of signals.

To ensure and evaluate the quality of their actions the most mentioned answer of the countries is the check of sales or consumption data of the relevant drug. But this data is not for all agencies available.

Other practices of several agencies are:

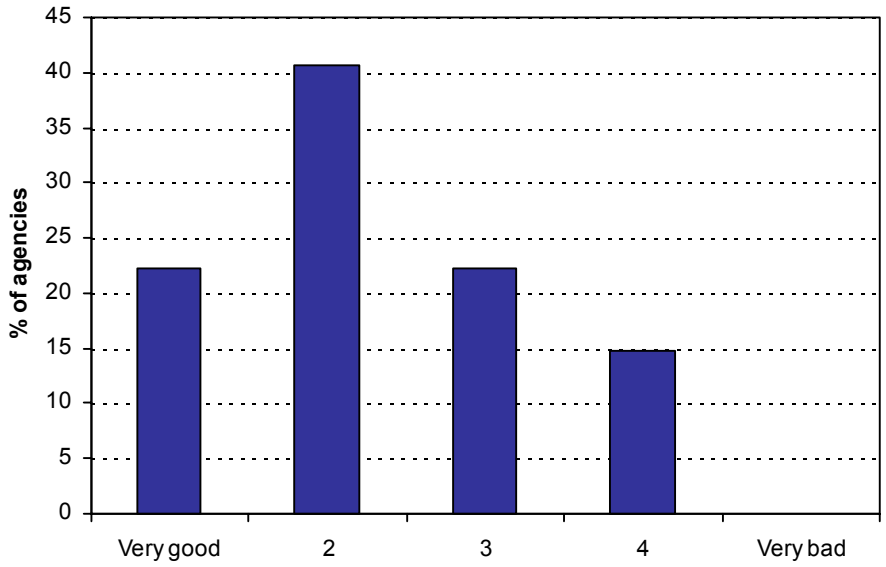
- peer review by ministry/director etc.
- check of variations in SPC
- consultation with scientific experts
- consultation with international stakeholders

Only in 9 of the 27 answering agencies there is an audit procedure for the different steps or pharmacovigilance. 21 agencies state that their audit procedures do not adequately ensure the quality of their work.

An average of four scientific publications with at least one author from the agency were published in the last year by each of 23 responding agencies.

It was asked how well the agency meets its internal targets for timing and other requirements. The results are presented in Figure 3.33

Figure 3.33. Meeting of internal targets



Source: Fraunhofer ISI 2005

Of 21 agencies, the compliance with their 15day obligation of reporting to EMEA or to MAHs is nearly perfect in 62% and high in 19% according to their self-reports in the agency survey. It is only medium or low in 19% of the agencies. Follow-up information is not transmitted within 15 days by 52% of the agencies.

The internal cooperation within the agency (within PhV unit, with pre-marketing department, incl. IT staff) is assessed as very good or good in 93% of the agencies. The cooperation of the agency with HCPs is very good or good in only 68%, and the cooperation of the agency with the MAHs is very good or good in 93% of the agencies.

The compliance of MAHs with expedited reporting is routinely checked in 41% of the cases, the MAH's compliance regarding PSURs is only checked in 56%.

Action in the case of non-compliance is taken in 52%. Such actions are e.g. warning letters, inspections, and financial penalties.

3.6.1 Training of the staff

Personal training, e.g. in research methods or database-administration is not a very frequent means of quality assurance. In 8 of the 28 agencies the whole staff attended at least one training in 2004. An average of 50% of the staff received a training measure in the last year. In the opposite there are 7 countries where less than the quarter of a personal attended one. So there are huge differences in this topic, which are not solely explicable by the size of the countries.

3.6.2 Education of reporters

In the average country, 5 events have taken place in the last year with participation or support from the Agency to educate reporters/HCPs in pharmacovigilance?

3.7 Phases of pharmacovigilance

The combined results of the interview and questionnaire survey at the agencies are presented in the following paragraphs according to the phases of pharmacovigilance (Data collection, data management, signal detection, safety issue assessment, decision-making, and communication and action to protect public health).

3.7.1 Data collection

Each national pharmacovigilance centre should have a system in place that allows the receipt, management and evaluation of all pharmacovigilance data within that Member State in a way which is compatible with the procedures undertaken in the other Member States and the EMEA ("Volume 9", updated July 2004, p. 65).

Data to be collected are in the first line spontaneous reports on suspected adverse reactions (ICSRs) from MAHs and from HCPs, as well as PSURs from MAHs. In the following we call the combination of these two sources "routine data". Reports can be made in writing (e.g. using report forms), by telephone, electronically, or by any other approved way.

3.7.1.1 Spontaneous reporting

Reporting of suspected ADRs is mandatory for healthcare professionals in 17 of the answering 26 countries, in general for physicians and pharmacists, in AT e.g. also for dental surgeons and midwives, in EE also for doctors, nurses, midwives, and dentists, in ES, IT and SL also for all other types of Health Care Professionals. In Germany, reporting is not obligatory by law (except for ADRs following vaccination and blood products), but by a self-commitment of physician's associations. In IT reporting is mandatory for all suspected serious and unexpected non-serious ADRs for all drugs. In addition for vaccines and for those drug included in the "intensive monitoring scheme" reporting of all ADRs is requested.

On the other hand, an independent report of the UK spontaneous reporting system published in April 2004 considered whether there should be a legal requirement to report ADRs. Published data do not support a better reporting rate in countries that have mandatory schemes compared to those that do not9. Because of this and the practical difficulties of enforcing such a law the review did not recommend the introduction of mandatory reporting in the UK.

Absolute numbers of reports

As the following table shows, as of July 2005, the reports are generally submitted on paper to most of the agencies. Exceptions are IT and LV, where 90% and 50% of the reports come via the web-site, respectively. 10 or more percent are already submitted electronically in BE, FI, IC, LT, LU, and PL with a exceptionally high 80% of electronically submitted reports in SL.

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9 Hughes ML, Whittlesea CMC and Luscombe DK. Review of national spontaneous reporting schemes. Adv Drug React Toxicol Rev 2002 21 (4): 231-241

Table 3.15. Submission of reports on ADRs [% of ICSRs] as of July 2005

	On Paper	Electronically	Via web-site	Other
AT	99	.	.	1
BE	90	10	0	.
CY	90	0	0	10
CZ	98	1	0	1
DE-BFARM	100	0	0	0
DE-PEI	100	0	0	0
DK	93.80	2.60	2.60	1
EE	90	.	10	.
EI	99	.	.	1
ES	95	.	2	3
FI	85	15	.	.
FR	95	1	1	3
HU	95	5	0	0
IC	80	20	0	0
IT	10	0	90	0
LI	.	.	0	0
LT	80	20	0	0
LU	80	20	.	.
LV	50	.	50	.
MT	100	0	0	0
NL	82.50	2.40	15.10	0
NO	100	0	0	0
PL	90	10	0	0
PT	100	0	0	0
SE	100	.	.	.
SL	20	80	0	0
SV	100		0	0
UK	94	3	3	0

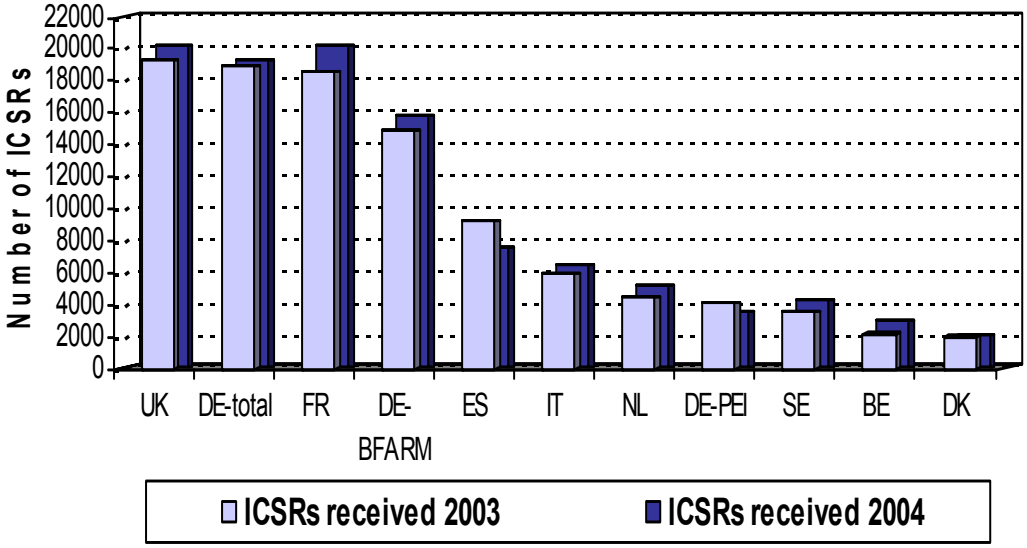
Source: Fraunhofer ISI 2005

For reporting, some countries have a specific form, often called "yellow card", but also accept the standard CIOMS and other forms.

Incomplete ICSRs, i.e. ICSRs submitted with less than 4 minimal data points are rare in the most countries with a mean of 0.72% of incomplete reports; the data quality is acceptable for 23 of 27 respondents.

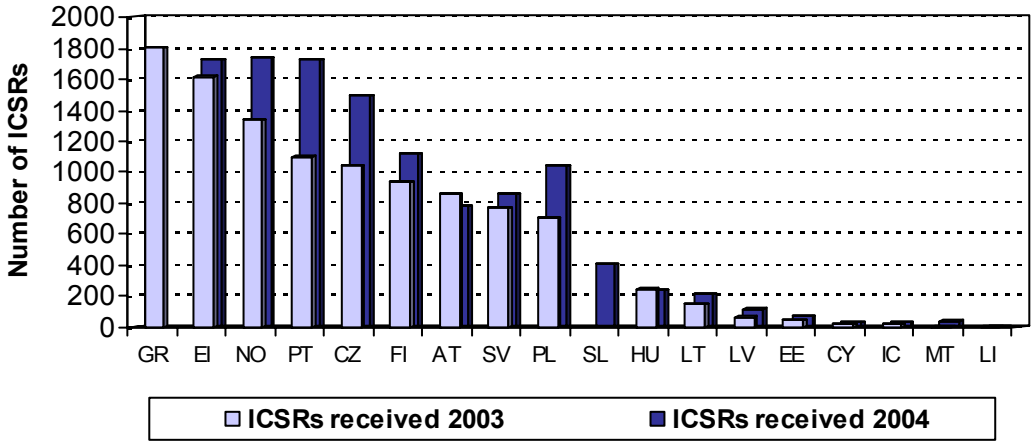
Figure 3.34 and Figure 3.35 give the absolute numbers of ICSRs that were received by the national agencies in 2003 and 2004. The related relative indicators ("reporting rates") are more useful to assess the performance of the system than these absolute numbers. The relative values are presented in Table 3.17 and Figure 3.38, Figure 3.41 and Figure 3.42).

Figure 3.34. ICSRs received 2003 and 2004 (countries with numbers of ICSRs ≥2000)



Source: Fraunhofer ISI 2005

Figure 3.35. ICSRs received 2003 and 2004 (countries with numbers of ICSRs <2000)

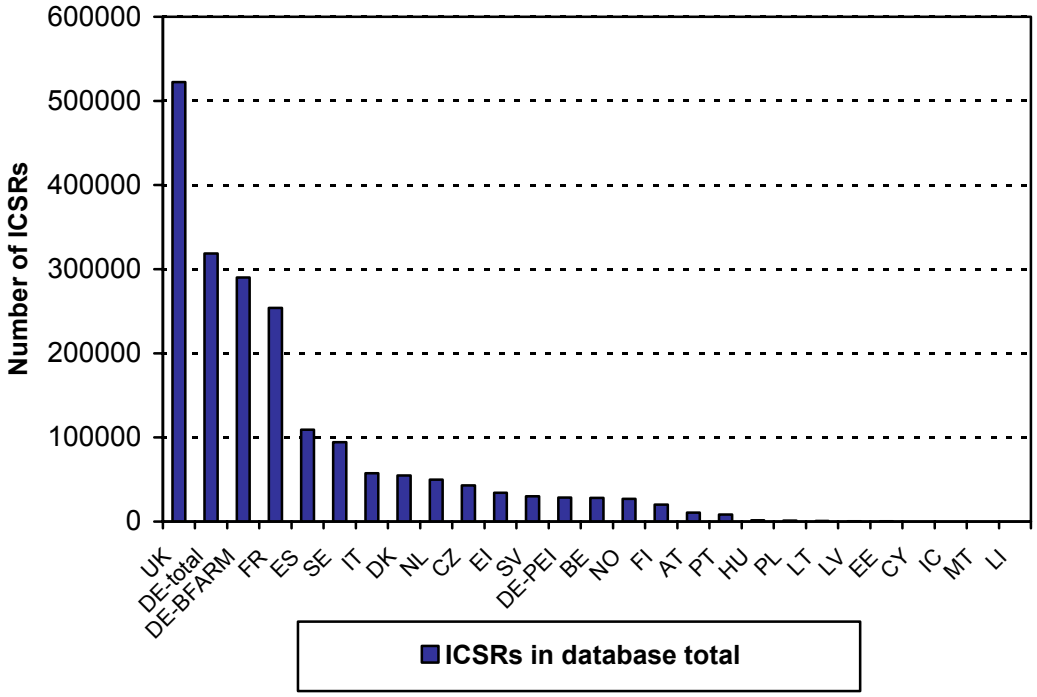


Source: Fraunhofer ISI 2005

The numbers of ICSRs received generally rose between 2003 and 2004.

The total number of ADR reports that have been accumulated over the years in the national databases heavily depends on the size of the country (Figure 3.36), but also on the policies of transferring old reports into the new databases and when data started to be collected.

Figure 3.36. Total number of ADR reports in the national databases



Source: Fraunhofer ISI 2005

In 2004, more than half of the suspected ADRs were submitted by doctors or dentists, followed by ADRs from MAHs. Other groups played a minor role, in most countries no reports were received from nurses, patients, coroners, or professional bodies (Table 3.15).

Table 3.16. Suspected ADRs from reporter groups

	% [Median]
Doctors/dentists	52.05
MAHs	37.29
Others	3.27
Pharmacists	1.80
Nurses	.00
Patients	.00
Coroners	.00
Professional body	.00

Source: Fraunhofer ISI 2005

Particularly high (i.e. >70%) are the shares of ADRs from MAHs for the following agencies: LI (100% of ADRs from MAHs), DE-BFARM (83%), BE (75%), and DE-PEI (74%), whereas in IC 96% of ADRs come from doctors/dentists (DK: 92%; SV: 95%; IT: 87%; SE: 87%; FI: 77; and NO: 71% from doctors/dentists).

Reporting by size of the population

The reporting rates computed by number of received ICSRs divided by the population size differed greatly. They are presented in Table 3.17 along with the figures from the two ERMS surveys.

Table 3.17. Reporting rates – different indices

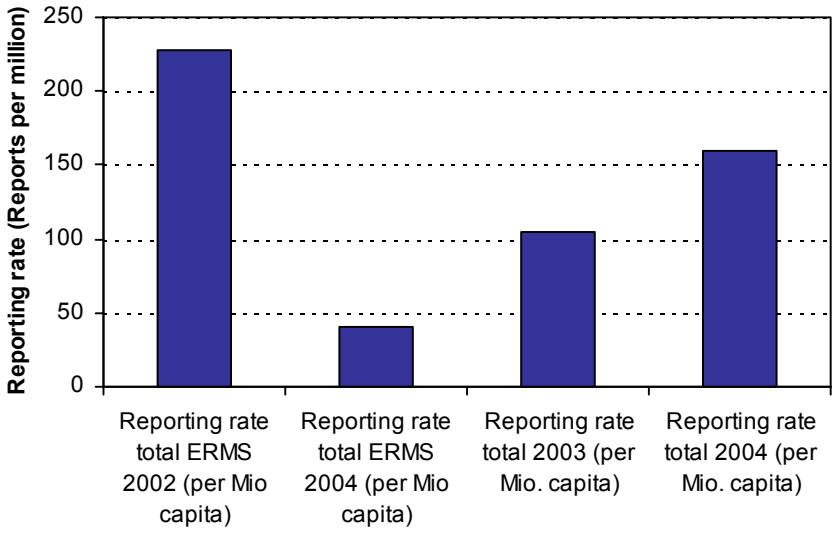
	Rep.-rate total (p.Mio) ERMS 2002	Rep.-rate total (p.Mio) ERMS 2004	Reporting rate total (p.Mio.) 2003	Reporting rate total (p.Mio.) 2004	Rep.-rate children (p.Mio) ERMS 2002	Rep.-rate children (p.Mio) ERMS 2004	Reporting rate children <=19 (p.Mio.) 2004
Valid cases	13	9	25	27	11	1	23
Median	228.0000	40.0000	105.3531	159.8483	51.0000	9.5000	63.4622
Minimum	55.00	18.20	.00	23.13	4.20	9.50	.00
Maximum	458.00	145.70	402.98	459.46	288.00	9.50	406.85

Source: Fraunhofer ISI 2005

Reporting rates for the total population were smaller (Md=40.00 reports per million inhabitants) in the new MS in 2004 (column "Rep.-rate total (p.Mio) ERMS 2004") than in the old MS in 2002 (column "Rep.-rate total (p.Mio) ERMS 2002": Md=228.00 reports per million inhabitants). Taken together the rates computed from the own data in 2003 and 2004 (3rd and 4th column), the rates increased from

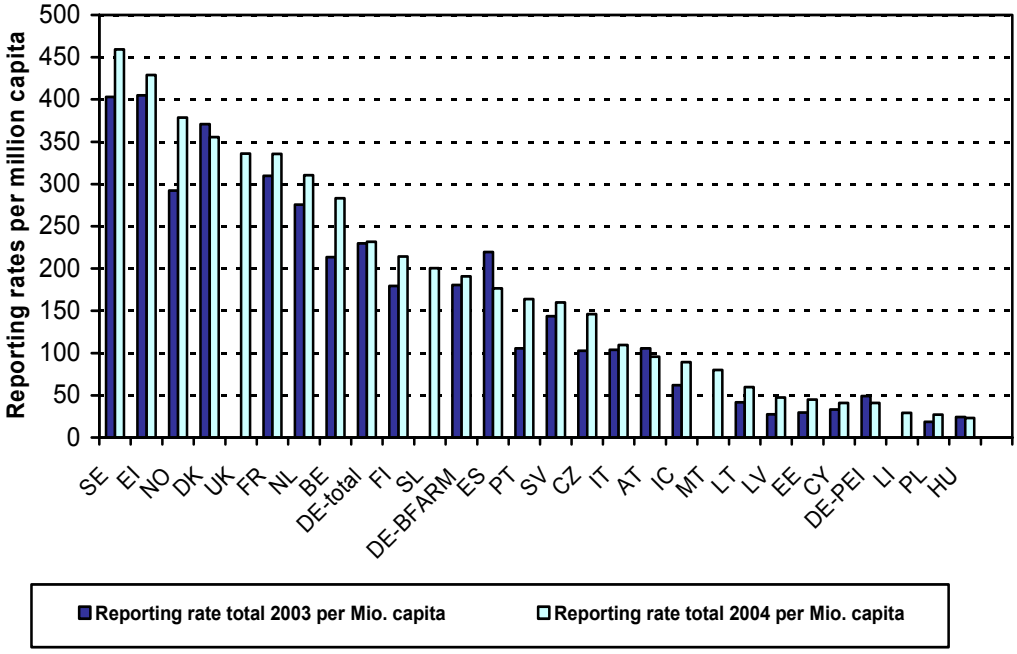
105 to 159 per million, but could not reach the old level of the year 2002. However, an influence of possible differing computation methods cannot be ruled out.

Figure 3.37. Reporting rates for total populations over time, number of ICSRs divided by population size



Source: Fraunhofer ISI 2005

Figure 3.38. Reporting rates for total populations 2003 and 2004, number of ICSRs divided by population size

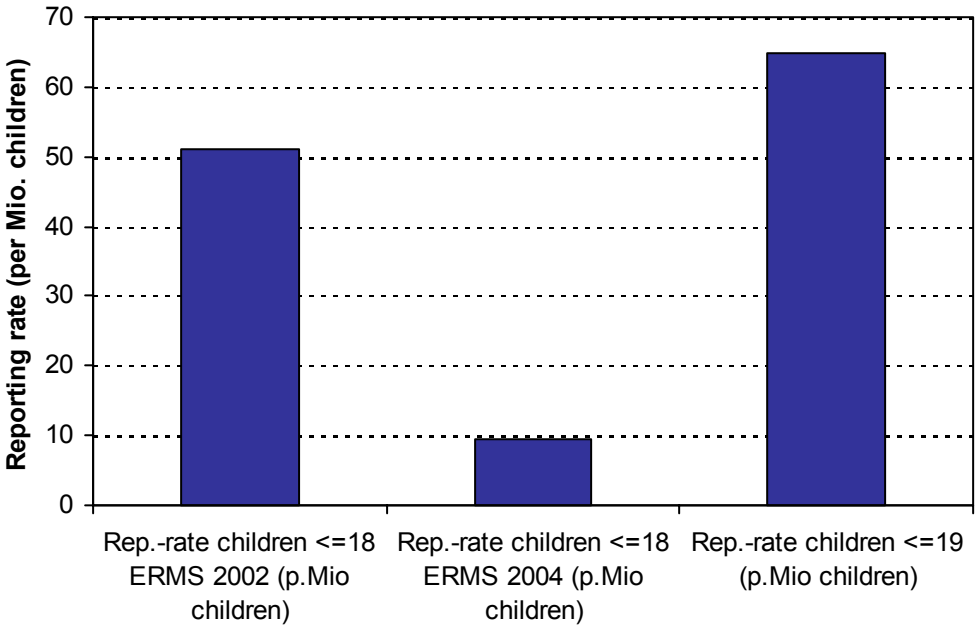


Source: Fraunhofer ISI 2005

The highest reporting rates (2004 total population) can be found in Sweden, Ireland, Norway, Denmark, the UK, France, and the Netherlands. In most countries, the rates increased between 2003 and 2004.

The reporting rates for children are far lower than those for the whole population, which could be a result of lower incidence of diseases and lower consumption of pharmaceutical products in children. In 2004, an average rate of Md=63 reports per million children was computed, however also with a small bias because reports were counted by the agencies for children and adolescents less than 18 years of age, but the population sizes could only be found for the EU and EEA Member States for persons up to 19 years (Eurostat). The respective figure for the total population was Md=160 reports per million inhabitants (Table 3.17).

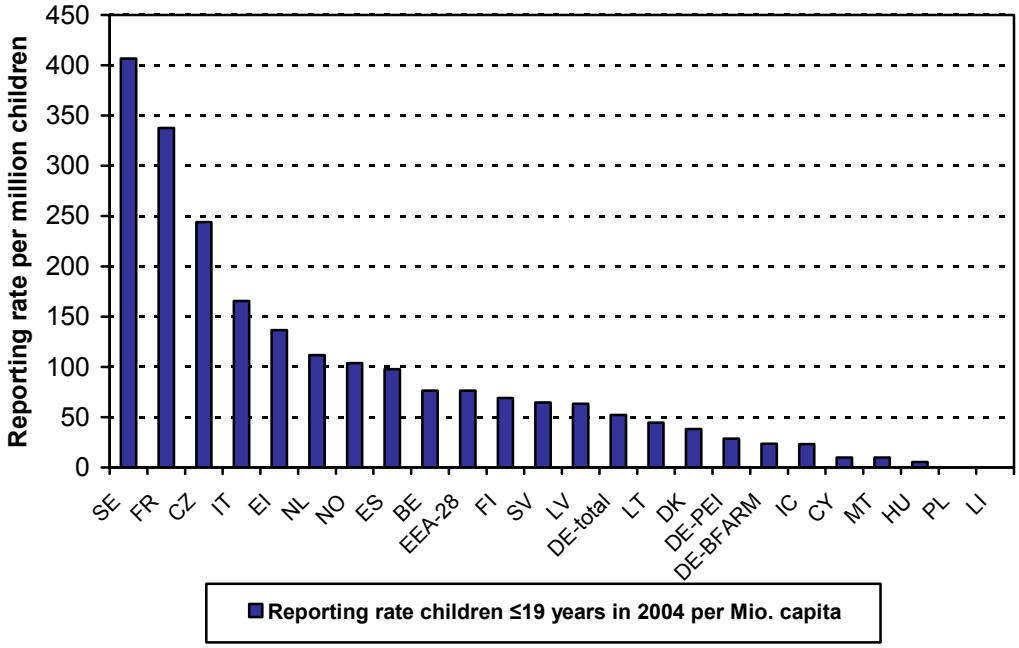
Figure 3.39. Reporting rates for children over time, number of ICSRs 2004 divided by number of children



Source: Fraunhofer ISI 2005

The differences can be explained by the different samples that were assessed between the ERMS-2002 survey (old MS), ERMS-2004 (new MS) and the total sample of the own agency survey in the third column.

Figure 3.40. Reporting rates for children ≤19 years, number of ICSRs 2004 divided by number of children



Source: Fraunhofer ISI 2005

Sweden, France, the Czech Republic, Italy and Ireland have extraordinarily high reporting rates for children compared to other countries.

Reporting by type of product

The following table presents the numbers of ICSRs that the agencies received in their different roles as responsible agency for nationally authorised products (NAPs), as concerned MS for products licensed through the mutual recognition procedure (MRPs) and as Reference Member State for MRPs. Most products are authorised as NAPs (a median of 4286 products per country), the second most are MRPs (Md=406 per country), the least are CAPs (269 in all countries), therefore it is not astonishing that most of the received ICSRs in absolute numbers are received for NAPs.

Table 3.18. ICSRs by MA procedure

	Median	Minimum	Maximum
ICSR on NAPs	234.00	1.00	8050.00
ICSR as concerned MS	10.00	0.00	8500.00
ICSRs as RMS	0.00	0.00	4100.00
→ **National ICSRs per NAP**	0.05	0.006	1.31
→ **ICSRs as concerned MS per MRP**	0.03	0.00	2.98
→ **ICSRs as RMS per MRP**	0.00	0.00	1.03

Source: Fraunhofer ISI 2005

On average (Median), 234 ICSRs were received by each agency on NAPs, 10 on MRPs with the respective country as concerned MS, and 0 on MRPs with the country as RMS. The variances are substantial in these figures. Relative to the numbers of products on the market, the reporting rate was best for NAPs (0.05 reports per nationally authorised product), second best for ICSRs as concerned MS per MRP (reporting rate = 0.03), and least for ICSRs as RMS per MRP (reporting rate = 0.00). The low median for ICSRs concerning MR products for which the country is RMS is certainly due to the fact that many of the participating agencies have not yet been a RMS and therefore had to answer "0 reports received as RMS" in the survey.

Reporting by market size

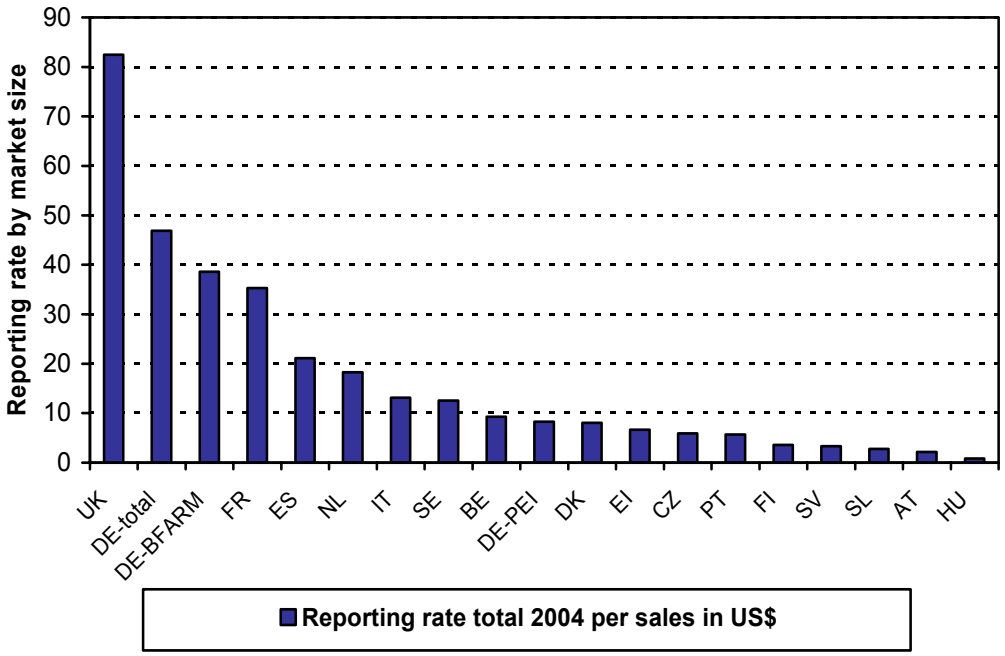
The number of submitted reports will certainly depend on the sold volume of pharmaceutical products (the market size), which is here measured as the countries' pharmaceutical sales in US$ (source: WHO-EURO HFA-DB; http://data.euro.who.int; those numbers of 2002).

Table 3.19. Reporting rates for total populations, number of ICSRs divided by pharmaceutical sales in the respective country

Indicator	Reporting rate total 2003 per sales in US$	Reporting rate total 2004 per sales in US$	Reporting rate children <=19 2004 per sales in US$
Valid n	20	18	16
Mean	15.4439	17.6737	2.2664
Median	7.6668	8.7678	1.3999
Minimum	.00	.79	.00
Maximum	79.21	82.49	9.05

Source: Fraunhofer ISI 2005

Figure 3.41. Reporting rates for total populations; number of ICSRs 2004 divided by pharmaceutical sales



Source: Fraunhofer ISI 2005

Reporting by number of physicians

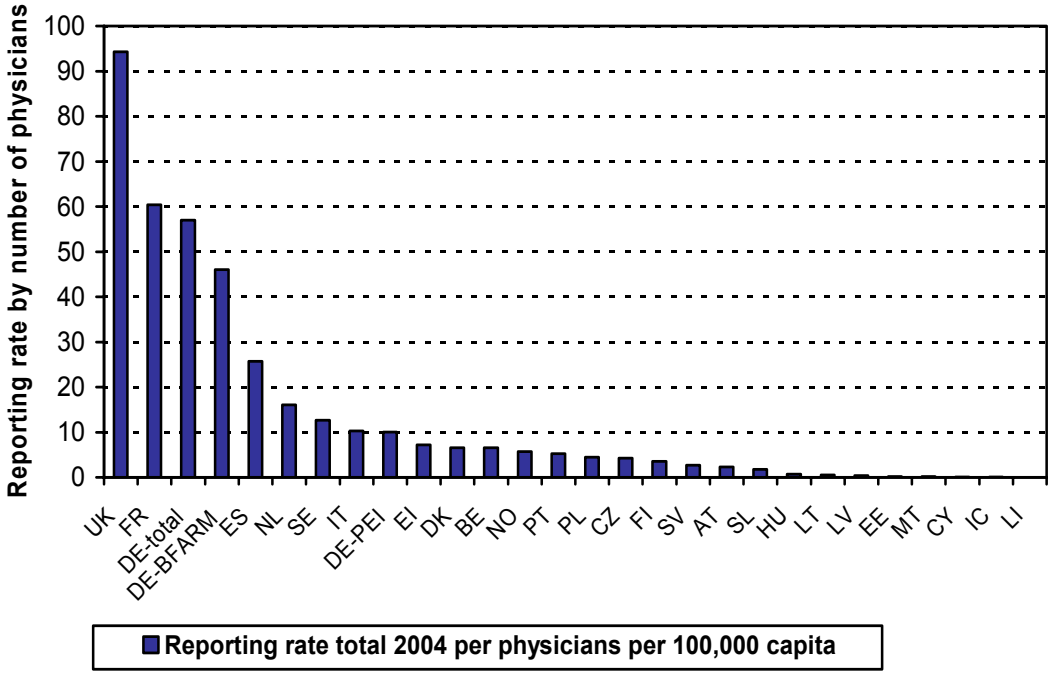
The following table gives the reporting rates that are standardized by the number of physicians in the respective country. It can be seen that the average (median) values increase between 2003 and 2004, but that huge differences exist between the countries with the minimum rates and the maximum rate. As it can be expected, the reporting rate for children is again lower than the rate for the whole population.

Table 3.20. Reporting rates for total populations, number of ICSRs divided by number of physicians

Indicator	Reporting rate total 2003 per physicians per 100.000 capita	Reporting rate total 2004 per physicians per 100.000 capita	Reporting rate children <=19 2004 physicians per 100.000 capita
Valid n	27	27	25
Median	3.38	4.51	.41
Minimum	.00	.01	.00
Maximum	90.53	94.28	20.83

Source: Fraunhofer ISI 2005

Figure 3.42. Reporting rates for total populations, number of ICSRs 2004 divided by number of physicians



Source: Fraunhofer ISI 2005

3.7.1.2 Underreporting

According to the agency interviews, underreporting is a problem in many countries, especially in the smaller Member States, but no valid estimates are available that are comparable between the countries.

The most important reasons for underreporting are

- lack of time of the reporters (11 responses in the 27 interviews),
- economic reasons/missing incentives (7 responses),
- lack of education (9 responses),
- being afraid that wrong treatment could be revealed (8 responses) and
- a negative attitude towards reporting (5 responses).

Less often mentioned were missing interest, administrative workload, missing legal obligation to report, missing electronic system for reporting and technical reasons, and cultural or traditional reasons.

Interesting aspects on reporting rates are related to the market structure: In one country the domestic MAHs produce only generics which are perceived as safe; in addition, the MAHs do not send sales agents to doctors to collect ADR reports in this country, and have many OTC drugs and therefore do not work with physicians,

factors which all will reduce the reporting. Another assumption is that HCPs can be disappointed because of missing perceived action based on their report. In addition organisational and technical reasons exist for low reporting, the system is not yet simple enough, and – as one interview partner in an agency assumed – MAHs might use their influence on doctors in order to reduce reporting e.g. by giving them simplified information on ADRs.

3.7.1.3 PSURs

Periodic safety update reports (PSURs) are the periodical reports that the MAHs have to submit to the concerned agencies containing the ICSRs they have received in the last period as well as other safety-relevant information referred to in Article 104 of Council Directive 2001/83/EC.

The total number of PSURs received varies between a maximum of 2940 in one country and no single PSUR received in three countries.

Table 3.21 gives an overview on the PSURs that are received by the agencies according to the different authorisation procedures.

Table 3.21. PSURs by MA procedure

	Median	Minimum	Maximum
Natl. PSURs received	517.50	0.00	2500.00
National PSURs per million capita	42.1482	0.0000	228.5271
National PSURs per NAP	0.0707	0.0000	2.4604
PSURs received as RMS	11.50	0.00	675.00
MR PSURs as RMS per million capita	0.2032	0.0000	64.9263
MR PSURs as RMS per MRP	0.0243	0.0000	1.0000
PSURs received as rapporteur	11.00	0.00	370.00
CAP PSURs as rapporteur per million capita	0.4357	0.0000	23.1811
PSURs as rapporteur per CAP	0.0409	0.0000	1.3755

Source: Fraunhofer ISI 2005

On average (Median), 518 national PSURs were received per country, i.e. 42 per million population or .07 national PSURs per authorised NAP. PSURs for MR authorised medicines are received much less frequently, but are related to the number of MR drugs for which the country is Reference Member State. The number of PSURs is of the same magnitude, as is for PSURs per CAP for which the country is rapporteur.

In some countries, all of the received and even foreign PSURs are assessed, but in a few countries the percentage of assessed PSURs is below 10%.

3.7.1.4 Other sources of information

Other sources of information are analysed in addition to the ICSRs and PSURs.

20 of 25 answering agencies have access to databases: Besides Eudravigilance and the EMEA website, the UMC Vigibase[10] is mentioned most frequently (11 answers), followed by Medline[11] (8 answers). Some agencies have access to registries of products and drug consumption data. Other national registries (on birth, cancer, hospital admissions, GPRD…) exist, and also a clinical trial database is accessed.

The agencies were asked if there are other data that they are using or could use for signal detection or safety issue assessment in their country. The answers are summarized in Table 3.22. In its second column, the number of agencies is given which mention that a certain source exists in their country. The next three columns headlined by "Access" give the shares of agencies that have access to the source never, in exceptional cases or always. The last three columns describe the use of the source in similar categories as share of all responding agencies.

Table 3.22. Existence and use of population-based health/disease registries

	Exist	Access			Use		
	N of agencies	% never	% in except. cases	% always	% never	% in except. cases	% routinely
Cancer	24	13.6%	72.7%	13.6%	36.4%	59.1%	4.5%
Causes of death	23	12.5%	50.0%	37.5%	29.2%	58.3%	12.5%
Malformations newborns	22	9.5%	71.4%	19.0%	13.6%	77.3%	9.1%
Inpatient care	19	15.0%	60.0%	25.0%	36.4%	50.0%	13.6%
Outpatient care	14	21.1%	52.6%	26.3%	36.8%	47.4%	15.8%
Intrauterine drug exposure	11	31.3%	56.3%	12.5%	37.5%	56.3%	6.3%

Source: Fraunhofer ISI 2005

Except for outpatient care and intrauterine drug exposure, such registries exist in most of the countries. However, most agencies do only have access to these data in exceptional cases, and they are quite infrequently used.

The following table shows corresponding analyses for sales and prescription data.

[10] A database for ICSRs that is kept by the WHO at the Uppsala Monitoring Centre. At the moment, 77 counties worldwide submit reports to this database.

[11] A literature database in which many references from medical jounals are listed, hosted by the US National Library of Medicine with free access to references and abstracts.

Table 3.23. Existence and use of data on the consumption of medicines

	Exist	Access			Use		
	N of agencies	% never	% in except. cases	% always	% never	% in except. cases	% routinely
Sales data	24	0%	21.7%	78.3%	0%	33.3%	66.7%
Prescription non-hospital	19	14.3%	38.1%	47.6%	25.0%	40.0%	35.0%
Prescription by region	18	15.8%	42.1%	42.1%	35.3%	35.3%	29.4%
Prescription data only for reimbursed	16	15.0%	45.0%	40.0%	22.2%	55.6%	22.2%
Prescription hospital	14	31.6%	42.1%	26.3%	47.1%	23.5%	29.4%
Prescription by age	14	22.2%	44.4%	33.3%	31.3%	43.8%	25.0%
Prescription by sex	14	22.2%	44.4%	33.3%	31.3%	43.8%	25.0%

Source: Fraunhofer ISI 2005

Sales data exist in nearly all countries, less frequent are data on prescriptions made in hospitals. These data cannot always be analysed by age, sex, or geographical region.

Of all the data sources that are used in addition to the routine data, registries on cancer cases, causes of death and malformations of newborns exist in nearly all countries, to a lesser extent also databases on inpatient care. To all these sources, at least half of the respective agencies have access at least in exceptional cases. Data on malformations of newborns are used by nearly 90% of those who have access to such registries at least in exceptional cases, followed by causes of death data (71% of those who have access) and cancer registries (65%). Databases on outpatient care exist in only 14 countries, but if existing they are the data source that is used most frequently on a routine basis (16% of those agencies where outpatient data exist).

Among the usage data, sales data are available in nearly all countries and all of those have access at least in exceptional cases, nearly 80% always. These data are routinely used by nearly 70% of the countries where such data exist, the rest uses them at least in exceptional cases. Prescription data for outpatient care exists in 19 countries, but is restricted in most cases to prescription medicines. If data on sales or on outpatient prescription exists, the agencies normally have access to these data and three fourths of them use these data at least in exceptional cases.

Prescription data from hospital care as well as the differentiation of age or gender groups are less frequent. If existing, only one third of the agencies has unrestricted access and thus these data are used only by 25 to 29% of the agencies where such data exist.

Other data sources exist but are not used very frequently. The agencies mention here:

- Databases on primary healthcare outcomes and prescriptions (GPRD, IMS Health, PHARMO, General Drug Registry-implementation on-going)
- Disease-specific registries (Liver or kidney disorders, Diabetes, Infect. Diseases, Rheumatoid arthritis and treated patients, HIV infected and treated patients, organ transplantation, Case-control surveillance on blood dyscrasias, Cardiovascular Disease Register, rare paediatric diseases, Follow-up of rheumatologic patients exposed to biological products)
- Medical Birth Registry, maternity
- Surveys/studies (Children and youth survey, The Reykjavik Study, National Health Survey)
- Poison Centres
- Healthcare insurance register
- Health Protection Surveillance Centre
- Birth Register
- ISTAT
- IPCI data base
- Adverse events after vaccination
- Vaccination coverage, Post-vaccination reactions

In the ERMS-2002 survey, only 3 agencies, and in the ERMS-2004 survey only 4 agencies had plans to obtain some data sources at which they do not have access at the moment. In the new survey, 15 agencies mention that they plan to broaden their access to more data sources.

Seven agencies have the capability to link prescription registries with other registries which include health outcomes, and eight have experience in conducting pharmacoepidemiological studies using such data.

In total over all respondents, 432 pharmacoepidemiology studies, post-authorisation surveillance studies or phase IV trials have been carried out last year with a sample from their country, taken all sponsors together (in the survey it was not distinguished between public and private). The highest numbers of PM studies were found in the UK (No accurate figure available, the number is estimated at >100), ES (n=92), and HU (n=61).

Of all studies, 49 were initiated by an Agency, most of them in FR (12 of 16 French studies initiated by the Agency), followed by DE (11 studies initiated by on of the two German Agencies).

15 of 26 evaluate reporting rates calculated from spontaneous ADRs and usage data.

In eight countries, ad-hoc pharmacoepidemiological studies were carried out in 2004 when a signal needed confirmation or quantification, in four countries studies for early PM surveillance of new products took place in 2004.

Clinical trial adverse event (AE) reports are collected by 21 authorities and are available to those staff responsible for pharmacovigilance of marketed products. Information is collected by 22 agencies on ADRs with compassionate use / named patient use of products.

Various literature sources are screened, the median is on a weekly basis. The most frequently used sources are presented in Table 3.24.

Table 3.24. Most important literature sources

	Number of agencies
Medline, Pubmed	17
Lancet	8
British Medical Journal	7
New England Journal of Medicine	7
Reactions Weekly	6
WHO database	5
Drug Safety	4
JAMA	4
Micromedex	3

Source: Fraunhofer ISI 2005

The following table shows, that in most agencies information on ADRs with compassionate use, on AEs in clinical trials, and on phase IV efficacy trials are routinely collected and recorded. Information from other regulatory authorities and on post-authorisation safety studies are collected less frequently, and only 10 agencies routinely record data/information on preclinical studies.

Table 3.25. Information collected

	N of agencies
ADRs with compassionate use	22.00
Clinical trial AE reports	21.00
Info phase IV studies	18.00
Info from other authorities	15.00
Info PASS	14.00
Info preclinical studies	10.00

Source: Fraunhofer ISI 2005

3.7.2 Data management

The collected data, especially the ICSRs, have to be stored, cleared from duplicates, checked for completeness, eventually transmitted to other stakeholders and prepared for analysis. In most agencies the ICSRs are stored in electronic databases in predefined format. Member States should ensure that data on suspected serious ADRs occurring in their territory are uploaded into the EudraVigilance da-

tabase. A sufficient number of comparable ICSRs is a prerequisite for the identification of signals by use of statistical tools especially for rare ADRs.

26 agencies use an electronic database to manage national ICSRs, four of the responding agencies do not. Very frequently agencies have developed their specific software systems for this purpose, although most of them and all of the more recent systems are E2B compliant and have a very similar functionality.

Duplicate reports are generally identified manually. 11 databases include audit trail functionality. 16 agencies convert old reports into ICH standards, three hold EU and Non-EU reports in their database. In all cases, all reports are accessible for the signal detection process either electronically or – if only very few reports are received in an agency – for manual analysis.

EudraVigilance is already in place in 15 agencies (as of July 2005). The standards for electronic transmission are implemented in 20 agencies. Some of the agencies use the WebTrader module of EudraVigilance.

Electronic reporting by the MAHs is in place in 11 agencies, in 2 agencies all reports are already transmitted by MAHs electronically; in two more agencies the share is more than 50%. If received electronically, the agencies can put the received reports automatically into their databases.

Paper reports are validated, i.e. checked with the reporter especially for serious cases and incomplete data or by cross-checks of the entered data with the case narrative in 21 of 27 agencies, electronic data in 14. Data can be aggregated in 20 agencies and the routine data and information from all the other data sources are readily accessible in 22 of 27 responding agencies (Table 3.26).

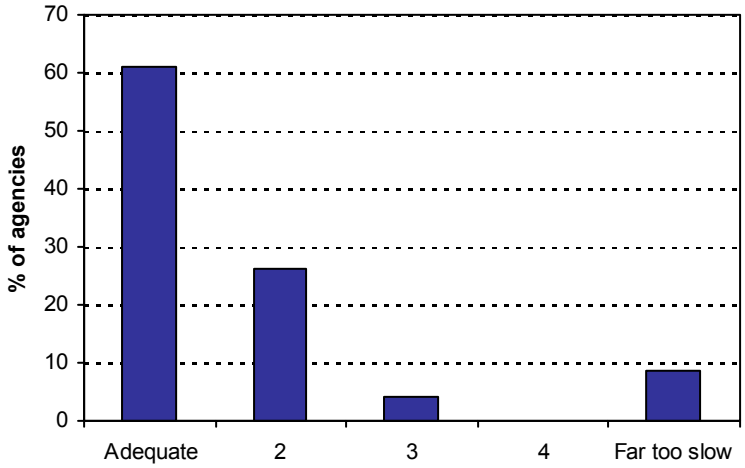
Table 3.26. Data quality

	N of agencies
Data validation paper reports	21
Data validation electronic data	14
Data aggregated electronically	20
Other data readily accessible	22

Source: Fraunhofer ISI 2005

The time needed for data processing is assessed as adequate by 14 of 25 answering agencies, but as "far too slow" by two of them (Figure 3.43).

Figure 3.43. Time for data processing



Source: Fraunhofer ISI 2005

3.7.3 Signal detection

Signal detection is the identification of probable adverse drug reactions on the basis of all available information. It includes an assessment of the causality of reported symptoms as most probably being an ADR. In general signal detection starts by the statistical analysis of ICSRs in the database.

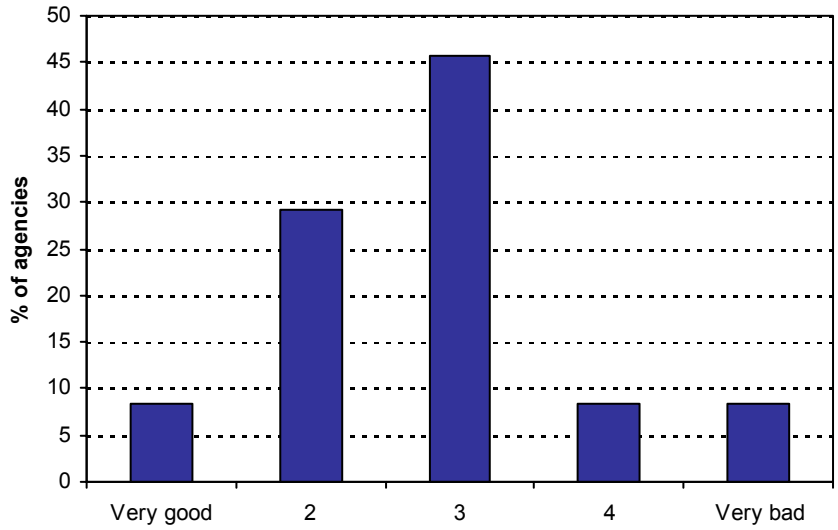
In the surveyed agencies, signal detection is carried out in different ways. In some agencies no specific procedure exists, some just mention ad-hoc-groups; others have elaborated procedures as e.g.

- A staff member gets each single report that falls into his area of expertise,
- The head of the department analyses each single report,
- A list of signals is produced by an IT-specialist once a month and is then discussed by the internal staff of the department (pharmacists, biologists, physician),
- The clinical assessors present reports at a weekly meeting in the agency which decides on measures, and a technical committee meets every month,
- Reports are sent to experts, they comment on what should be discussed at a meeting,
- Reports are assessed in the RCs.

Data are analysed statistically in 18 of the 27 agencies.

The agencies were asked in the written survey, "How do the MAHs in your country comply with their obligation to analyse safety signals?" Responding to this, the compliance of the MAHs with their obligation to analyse signals was assessed as moderate (Figure 3.44).

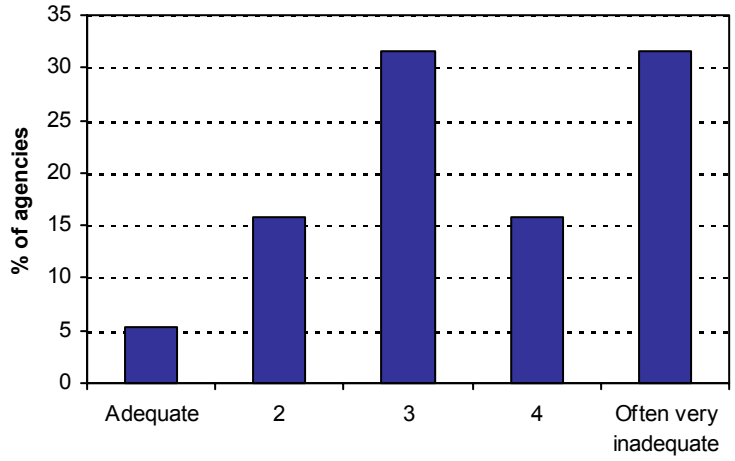
Figure 3.44. Compliance of MAHs in analysis of signals



Source: Fraunhofer ISI 2005

The following figure presents the evaluation of the statistical tools that the agencies have available for signal detection, assessed on a rating-scale with values from "always adequate" to "often very inadequate" (Figure 3.45).

Figure 3.45. Assessment of statistical tools for signal detection



Source: Fraunhofer ISI 2005

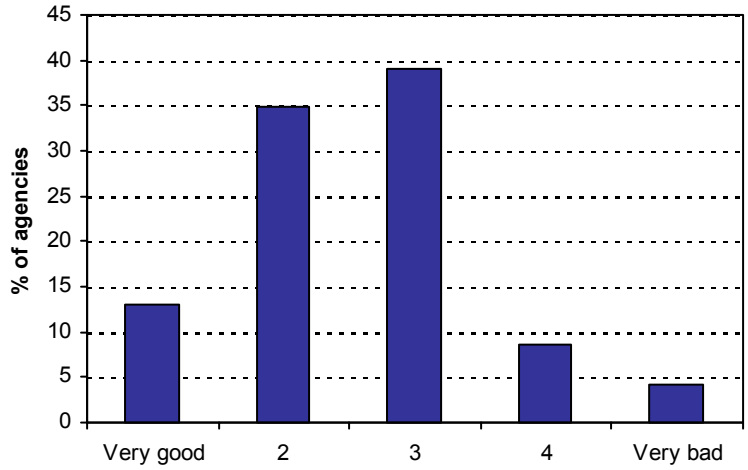
The evaluation is not very good, alone 6 of the 19 respondents assess the available statistical tools as often very inadequate.

Tools for the analysis of small numbers of reports have 13 of 25 agencies. A peer review system is in operation in 21 of 27 agencies. 20 of 27 agencies have a peer review system for the assessment of safety signals.

The agencies were asked, "How well has your routine data-collection prepared you for the last pharmacovigilance crisis?" Upon this question, only 35% of the agen-

cies found themselves very good or well prepared for the last crisis by their routine data-collection (i.e. (ICSRs and PSURs together; values 1 or 2 on a 5-point-rating-scale), but 40% found it only moderate and 13% bad or very bad (Figure 3.46).

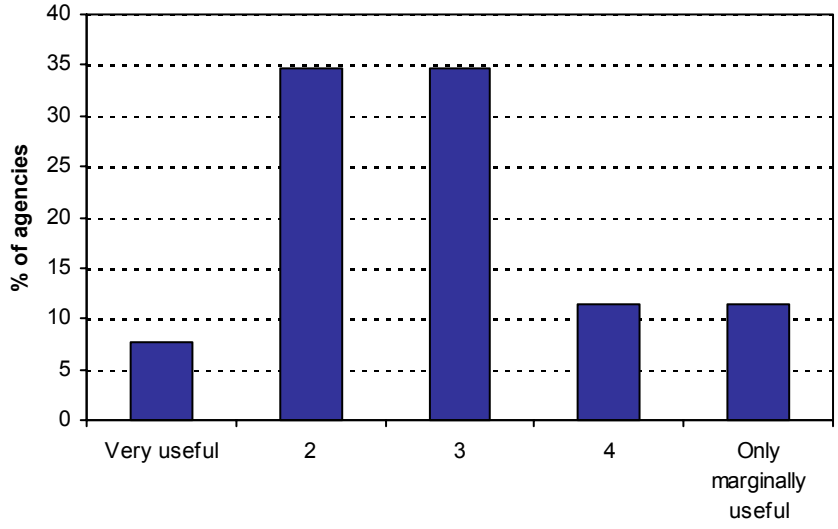
Figure 3.46. Preparation for last crisis by routine data



Source: Fraunhofer ISI 2005

The routine data are assessed to be very useful for safety issue assessment only by 2 agencies (7.7%), and useful by 35%. Only "moderately useful" (middle scale value) or even "only marginally useful" was answered by 48% of the agencies (Figure 3.47).

Figure 3.47. Usefulness of routine data



Source: Fraunhofer ISI 2005

70% of the agencies have not always had sufficient information to make decisions. When asked which kind of data they would you have needed in addition, the following data sources listed in Table 3.27 were mentioned.

Table 3.27. Informational needs for signal detection

Larger number of ICSRS
Information from other agencies • Assessment reports from abroad; • Info about reaction of other agencies (type, speed) • SPCs from other countries • Latest PSUR with benefit-risk evaluation
Basic research • Mechanisms of drug effects • Mechanisms of ADRs, pathomechanisms • Basic research on vaccines
Better access to literature
Pharmacoepidemiological data • Treatment-indications • Patient groups • Information on population • National/regional situation (access to treatment, e.g. how easy it is to get the drug …) • Outcomes • Epidemiological data with same diagnosis criteria for diseases / reaction • Epidemiological studies, epidemiol. comparisons • Incidences (by indications) • Comparator data
Registries, databases • Registries (on birth defects; poisoning centres; vaccines ;…) • WHO database • New registries for ADR-related diseases • Historical data, narrative • Information on old medicinal drugs • Combination of different databases, e.g. with morbidity data
Studies • Pre-marketing data • Clinical studies • PASSs • Evidence-based data; evidence on higher level of evidence hierarchy
Utilisation data • Usage data from the insurances • Utilisation studies: many done for the pricing/reimbursement • Prescription behaviour • Drug use data; drug utilisation research • Exposure data

Source: Fraunhofer ISI 2005

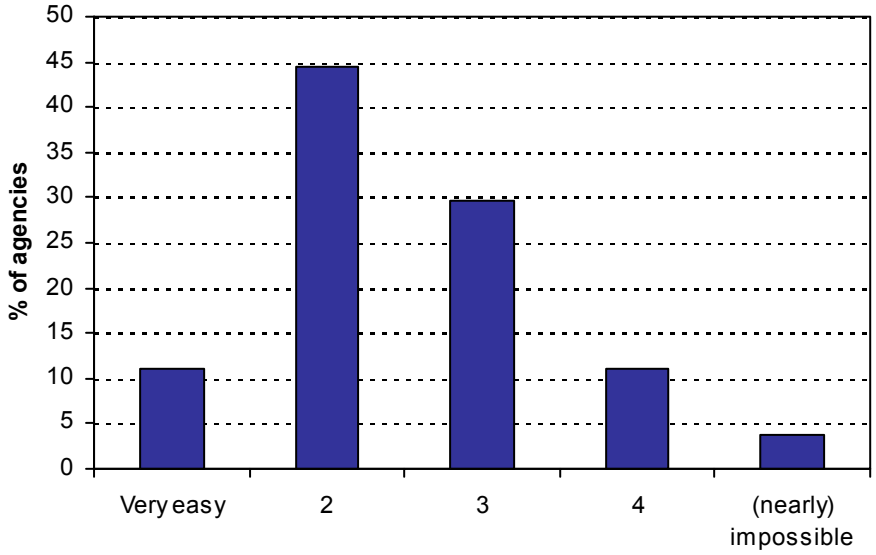
3.7.4 Safety issue assessment

Safety issue assessment has the task to evaluate the causality of a signal as an ADR and to appraise the severity and potential impacts on public health. This is normally done with support from or by an external expert committee.

External experts are routinely involved in safety issue assessment by half of the agencies; an expert committee to review safety assessments exists for 70% of the agencies. To receive support from external experts on a routine basis is generally

easy, but for 40% of the agencies it is difficult and for one agency nearly impossible (Figure 3.48).

Figure 3.48. Receive support from experts routinely



Source: Fraunhofer ISI 2005

To receive support from external experts in exceptional cases is even easier for the agencies than in routine cases, but only one third of the agencies get this support always when necessary.

15 of 29 agencies (52%) have the capabilities in their country to identify and assess signals without help from other agencies, also meaning that 48% or 14 agencies do not have this capabilities.

3.7.5 Decision-making

After the signal has been detected and identified as a safety issue it has to be decided if and what action should be taken. These decisions are often made upon advice from the pharmacovigilance staff or external experts by supervising bodies within the agencies of even by institutions outside the Medicines Agencies, e.g. in health ministries or by the European Commission.

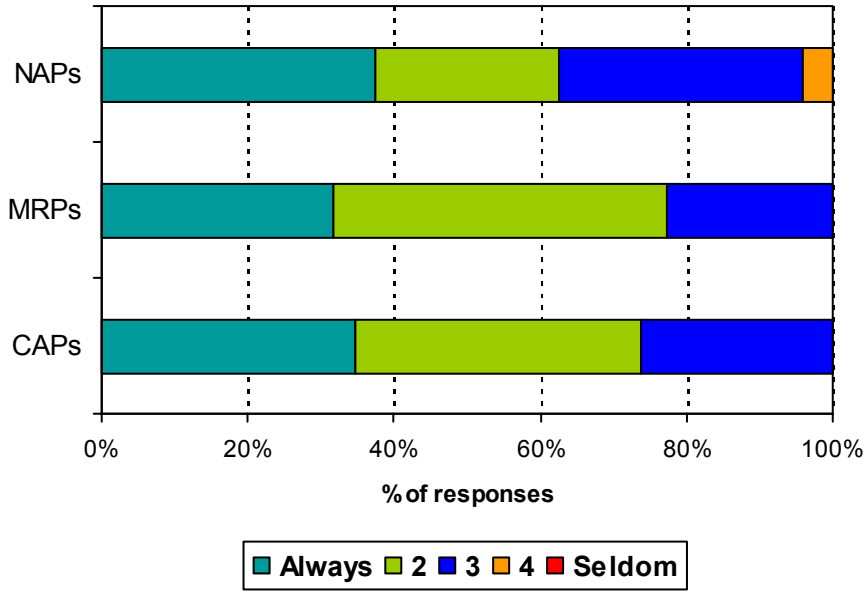
Decisions about actions are made by groups in 90% of the agencies, in general by agency-internal councils. The pharmacovigilance department prepares such decisions with support of the expert committees.

In about half of the agencies external stakeholders (doctors, pharmacists and patients) are involved in decision-making (in general as advisors or asked for comments on proposed decisions). In two agencies, the MAHs are consulted, in nine agencies other groups.

Decisions are based on a set of options and are recorded together with the reasons for them.

The agencies were asked how frequently adequate decisions are found for safety issues without explaining the word "adequate". 63% of the agencies find that adequate decisions concerning NAPS are always or often found. The respective value for MRPs is 77% and 74% for CAPs, respectively (Figure 3.49).

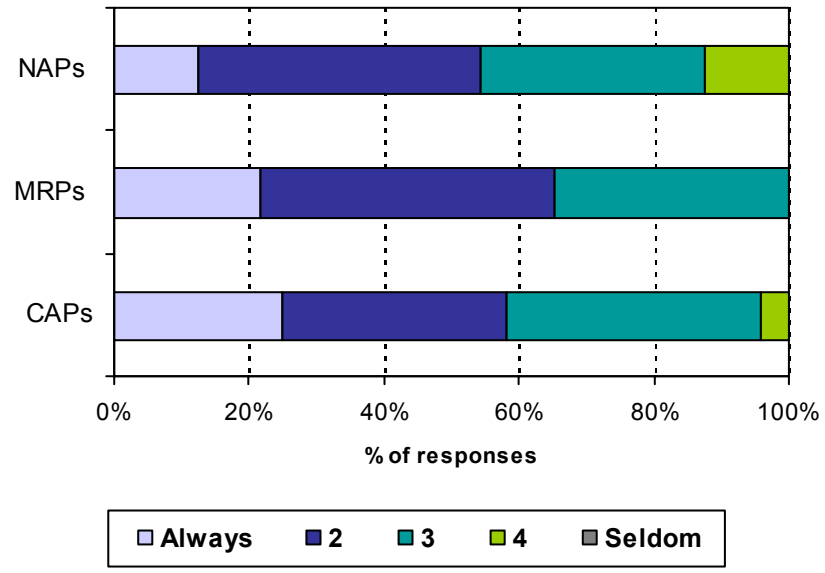
Figure 3.49. Adequate decisions found for safety issues



Source: Fraunhofer ISI 2005

The duration of the decision-making process was assessed fairly well for all three types of products (Figure 3.50). 54% find that decisions are found in good time for NAPs, 65% for MRPs and 58% for CAPs (assessment on a five-point rating scale from 1 "always" to 5 "seldom").

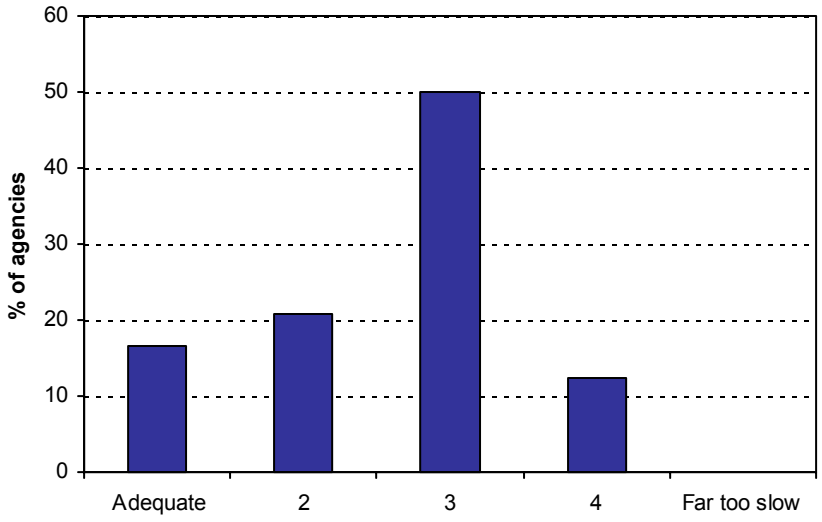
Figure 3.50. Decisions for safety issues found in adequate time



Source: Fraunhofer ISI 2005

The total time between the detection of a signal (first discussion within the agency) and reporting (publishing) of decision with respect to this safety issue (i.e. the time for the whole process of PhV) was assessed on a 5-point-rating-scale (1 'adequate'; 5 'far too slow'; Figure 3.52). The best or second best values were only chosen by 38% of the agencies, 50% assessed the velocity as "moderate", and 13% gave an even worse evaluation.

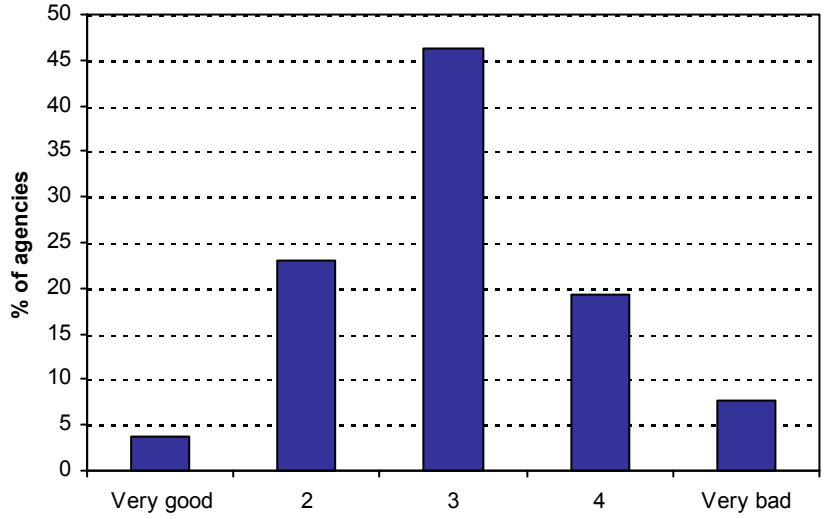
Figure 3.51. Kinetics of total process from signal detection and reporting



Source: Fraunhofer ISI 2005

The transparency of the process of decision-making on safety issues in the companies located in the country to the agencies was only assessed as moderate, and in 27% of the cases as bad or very bad (Figure 3.52).

Figure 3.52. Transparency of decision-making within the companies



Source: Fraunhofer ISI 2005

3.7.6 Communication and action to protect public health

If the competent body comes to the decision that a serious safety issue has been detected a number of measures can be taken to prevent further related ADRs and protect public health. The range is from informing HCPs and other competent authorities about the problem over changing the SPC by adding a new contraindication, e.g., to withdrawal of the product from the market.

Decisions are regularly published via press releases and on the internet. In addition, they are published for the concerned groups via bulletins, announcements in journals, communications to medical associations, Q&A documents for patients, and seldom on electronic networks. Sometimes, proactive information of the public is only done in outstanding cases and some decisions are only publicly available on request.

On average Md=6 bulletins with pharmacovigilance contents are published by the agencies per year (range from 0 bulletins in 5 agencies to 18 bulletins per year with an extreme value of 60 bulletins).

In the questionnaire we ask which stakeholder groups are routinely informed and informed on general and of specific safety issues. The results are presented in the following tables.

MAHs, individual doctors and pharmacists are routinely informed on general and specific issues by most of the agencies, followed by the public/media and medical associations. Professional journals and other HCPs are not so much in the focus,

and patient organisations and other groups seem to be underrepresented (Table 3.28).

Table 3.28. Routinely inform on safety issues

	Inform on general safety issues	Inform on specific safety issues
	% of agencies	% of agencies
MAHs	92	100
Individual doctors	92	96
Pharmacists	83	96
Medical associations	71	88
Public/media	61	92
Other HCPs	52	63
Professional journals	52	73
Other groups	26	53
Patient organisations	18	46

Source: Fraunhofer ISI 2005

The communication procedures that are in place in the agencies are described in Table 3.29.

Table 3.29. Communication procedures

	N of agencies
Procedures for crisis management	25
Systems for immediate communication	23
System for feedback to reporters	20
System to collect feedback	15
Procedures information/feedback	19
• **Information/feedback: info on web-site**	20
• **Information/feedback: bulletins**	16
• **Information/feedback: letters**	17
• **Information/feedback: e-mail**	15

n=27; Source: Fraunhofer ISI 2005

Although some of the interview partners stated that in general ADRs cannot always be prevented, many possible actions were mentioned that can be taken to prevent future ADRs (Table 3.30)

Table 3.30. Possible actions to prevent ADRs

Product interventions
• USR • Variation of SPC/PIL (Contraindications; warning; information about ADR/interactions) • Suspension of the MA • Withdrawal of the MA • Suspension of delivery • Withdrawal of specific lot
Collection of information
• Ask MAH for more information or to conduct post-marketing study • Record-linkage and registries with good recording • Risk management programme, Preauthorisation risk management planning, Pharmacovigilance-planning • Collaboration with insurance schemes
Provision of Information
• Press releases • DDL • Drug bulletin • Information of other agencies • Description of ADRs in the Formulary • Publish SPCs on internet-site • Contact to physicians in hospitals via chief physicians (=nominated contact points) • Educate prescribers on annual pharmacovigilance symposium
Market interventions
• Move product from OTC back to prescription • Marketing interventions (pack size…) • Restrict advertising (e.g. for OTC) • Change of availability (e.g. only in pharmacies, prescription only by specialists)
Other interventions
• Inspections including a person of the pharmacovigilance department

Source: Fraunhofer ISI 2005

A number of common and singular interventions were identified in the categories Product interventions, Collection of information, Provision of Information, Market interventions, and other interventions.

Frequently MAHs do not have to be forced but take actions voluntarily. The standard interventions were assessed by some interview partners as too few to prevent well-known ADRs. A suspension of the MA that is only possible for 3 months was seen as too short and is therefore not used very often.

In one country most drugs are only available through pharmacies, which was seen as an advantage because therefore the agency via the HCPs has better influence on consumption than with OTC drugs.

Actions as e.g. the provision of actual information can be implemented within few hours after an ADR has been detected. They are communicated in general to the other agencies within Europe, to MAHs, doctors, pharmacists and the media, and to a smaller extend also to patients and authorities outside the EU.

Actions implemented in the last year are shown in Table 3.31.

Table 3.31. Regulatory actions

	Median of actions per agency
Letters to MAHs to amend SPCs	50.00
Occasions DDL sent to HCPs	9.50
Drugs withdrawn from national market	3.00
Inspections of MAHs PhV issue	.00
MA suspended on national market	.00

Source: Fraunhofer ISI 2005

The range of withdrawals of MAs was from 0 to 769, for suspensions from 0 to 120 and for inspections from 0 to 51 per agency.

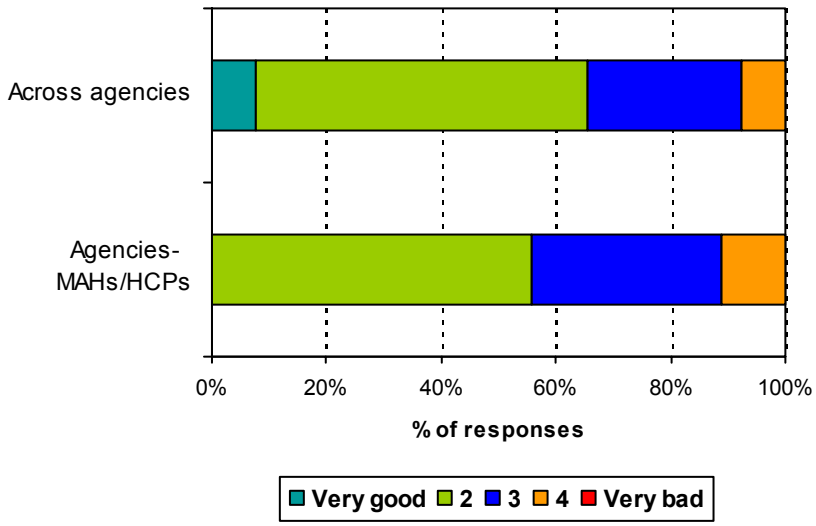
In addition, an average of Md=300 variations of SPCs were evaluated per agency, with a maximum of 10566 variations of SPCs.

A median of 91.5 responses to requests by HCPs were given per agency in the last year.

Only 8 agencies out of 23 respondents think that they always have the best measures to minimize risks from ADRs at their disposal.

The consistency of the communication on safety issues across agencies is evaluated as fairly good (Md=2 on a 5-point-rating-scale; Figure 3.53). The same is true for the communication on safety issues between agencies on the one side and MAHs and HCPs on the other side.

Figure 3.53. Consistency of communications



Source: Fraunhofer ISI 2005

The impact of communications is only followed-up on a routine basis by four of 29 agencies.

3.8 Outcomes of regulatory action

In the interviews we asked if impact of actions is audited, (9 agencies answered "Yes"), if systems for capturing impact of regulatory action are in place (only in five agencies), and if peer review and internal/external audit for actions taken is available (in 11 agencies; Table 3.32). This can be done with help of a registry (if available), data on use, or by discussions with supervising bodies as the competent departments in the health ministries.

Table 3.32. Impact of regulatory action audited

	N of agencies
Impact of major actions audited	9
Systems for capturing impact of regulatory action	5
Peer review, internal/external audit of action	11

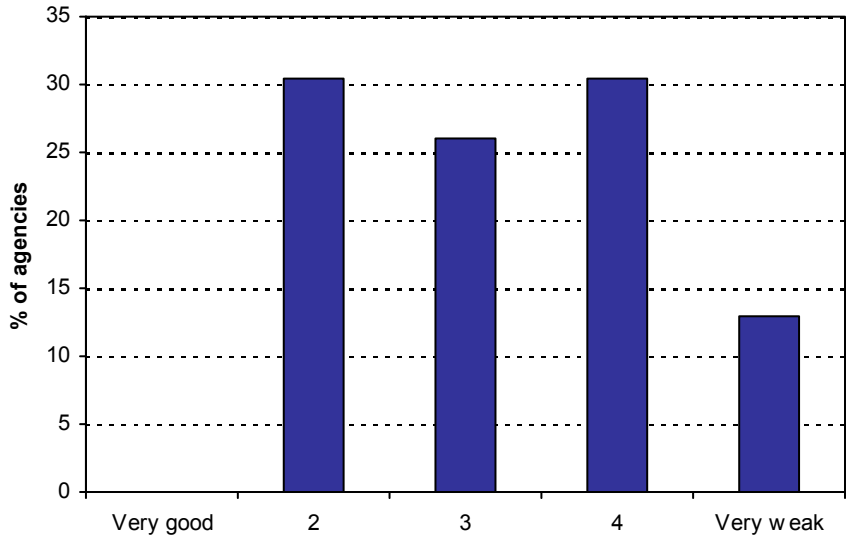
Source: Fraunhofer ISI 2005

A good way to monitor the effects of actions on prescription behaviour would be to monitor prescription/consumption data by drug classes or individual products on a monthly basis and compare the values before the action taken with the values after the action. This is already done by many agencies.

Other answers relate to evaluation of actions taken by the committee, ministry or the agency's board of directors, or consulting third parties. Other approaches are to check compliance by inspections, to check variations/changes in SPC, and case reviews after handling.

The influence of the agencies communications on the doctors' prescription behaviour is assessed as not very high (Figure 3.54).

Figure 3.54. Influence of agencies' communications on prescription behaviour



Source: Fraunhofer ISI 2005

In the agency questionnaire we also asked for the outcomes of safety-relevant studies (Incidence of ADR-relevant diseases; Mortality due to ADRs; Hospitalisations due to ADRs; Quality-adjusted life years (QUALYs) lost due to ADRs) although we know that these figures are not directly comparable across studies and countries.

However, 9 agencies stated that there are no studies with the incidence of ADRs as endpoint in their country, 10 stated that there was no study on mortality, 11 on hospitalisation and 13 on ADR-related loss of QUALYs (Table 3.33).

Table 3.33. Existence of outcome studies

	N of agencies	% of agencies
No Incidence Study	9	28.1
No Mortality Study	10	31.3
No Hospitalisation Study	11	34.4
No QUALY Study	13	40.6

Source: Fraunhofer ISI 2005

These figures seem to underestimate the number of countries in which no such studies exist because some additional agencies did not give information on any outcome studies either. Because so few studies were notified the outcomes cannot be analysed statistically. The following table contains the number of studies mentioned.

Table 3.34. Outcome studies

Number per country	Incidence studies	Mortality studies	Hospitalisation studies
Minimum	0	0	0
Maximum	5	4	6

Source: Fraunhofer ISI 2005

To allow cross-linkages of the results of the present study with international outcome figures, the following table presents the incidence of ADR-relevant diseases as published by the WHO.

Table 3.35. Incidence of ADR-relevant diseases

Country	Incidence of ADR-relevant diseases (per 100000)
EI	1.73
MT	1.67
FR	0.53
LU	0.38
ES	0.31
BE	0.19
SL	0.18
EU-25	0.13
EE	0.09
LV	0.09
IC	0.07
LT	0.07
PL	0.06
SE	0.06
UK	0.05
AT	0.04
CZ	0.03
FI	0.03
DE	0.03
IT	0.03
NL	0.03
DK	0.02
GR	0.02
HU	0.02
SV	0.02
NO	0.01
PT	0.01
CY	-
LI	-

Source: WHO-Euro (http://data.euro.who.int; numbers of 2002)

4 Goals in respect of effectiveness and efficiency

Initially it was intended to supplement a provisional list of goals related to effectiveness and efficiency of the European system of pharmacovigilance that was based on the literature by the respective results from the personal interviews with representatives of the competent authorities and representatives of the industry, and to ask the advisors in a Delphi-process to comment on the list. However, the interviews revealed nearly no new aspects in this respect; most of the interviewees found the actual scope of pharmacovigilance (with some modifications) in general sufficient, many referred to the related WHO definition according to which pharmacovigilance is

> *the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problems*[12].

Therefore, there was no need to elaborate more on the aspect of additional goals for pharmacovigilance in the project.

[12] WHO-UMC, see http://www.who-umc.org/defs.html

5 Critical success factors

Critical success factors are those elements of the whole process that determine its performance and can be modified to improve a system. The procedure for identifying and assessing the critical success factors was as follows:

Step 1:

For the 25 EU Member States and EMEA the most critical success factors for an effective and efficient functioning of the pharmacovigilance system (with respect to cost-effectiveness, time-efficiency, quality and safety) were identified on the basis of a systems approach supported by data from the interviews and literature. First results were discussed at the expert workshop on 15 June 2005. This first step resulted in a list of 75 draft factors which can be classified into the following categories (Table 5.1).

Table 5.1. Draft list of critical success factors

1. … for Data collection	**5. … for Decision-making**
1.1 Comprehensiveness of the data	5.1 Decision-making in legal bodies
1.2 Organisation of data collection	5.1 Decision-making in companies
2. … for Data management	**6. … for Communication/Action**
2.1 Electronic processing of data	6.1 Early communication
2.2 Processing of data	6.2 Communication to all stakeholders
3. … for Signal detection	6.3 Impact of communications/actions
3.1 Availability of necessary information	**7. … for performance in general**
3.2 Data analysis	7.1 Legal framework
3.3 International share of work	7.2 Staff
4. … for Safety issue assessment	7.3 General quality
4.1 Share of responsibilities	
4.2 Expertise	
4.3 Structures	

Source: Fraunhofer ISI 2005

Step 2:

After step 1, the advisors were asked in a Delphi-process to comment on the list of critical success factors. The experts rated these draft factors as well as the sub-

categories ("1.1 Comprehensiveness of the data" etc. in the list above) under the general question "Relevance: How important is the factor for the performance of the European System for Pharmacovigilance (or parts of it)?" according to their influence on the areas of

- quality of the work,
- compliance with requirements,
- speed ("kinetics"), and
- work load/costs

on five-point-rating scales.

The full results of the Delphi survey can be found in Annex 4.

Step 3:

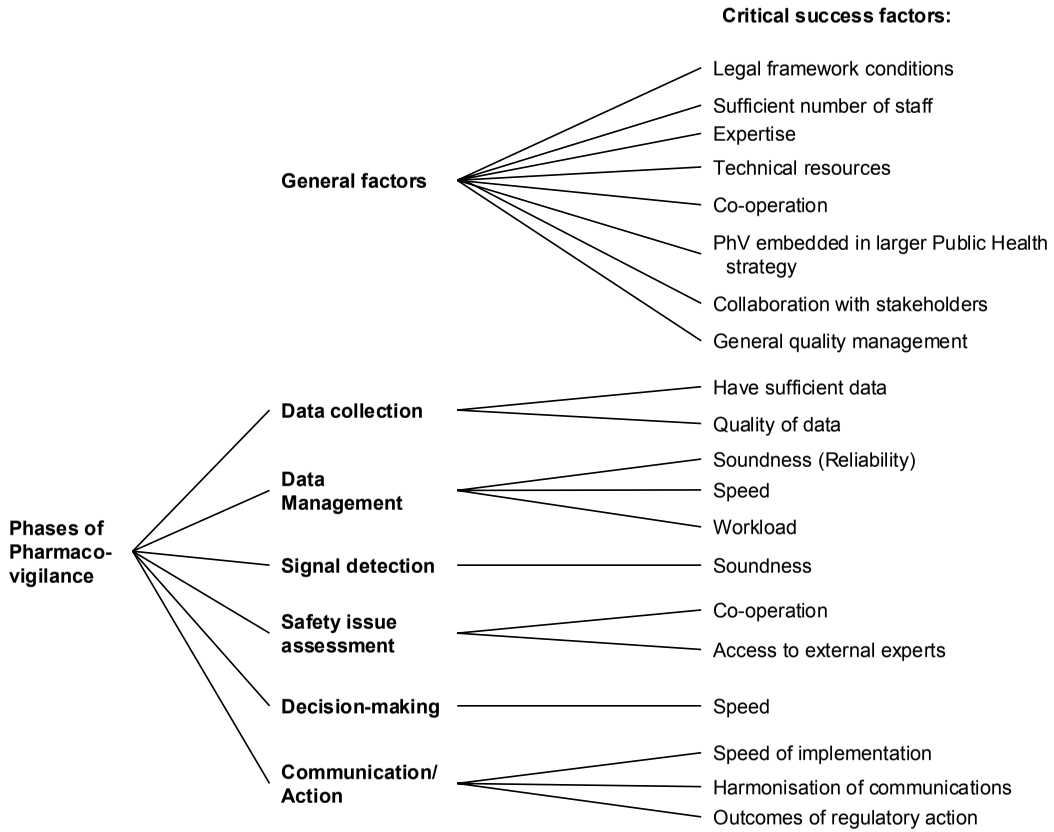
On the basis of the assessments of all draft factors as well as in reflection of the discussion of the factors at the expert workshop in Brussels on 15 June 2005, a selection of the most important, practicable and critical (in the sense that they can be modified from within the system) factors was made by the project team to achieve a concise list of the best factors. The resulting systematic of critical success factors is presented in Figure 5.1.

It was possible to identify a relatively concise list of one to three most important success factors for each of the six phases of pharmacovigilance. For data collection, it is most important to have sufficient and high quality data. Requirements of soundness, speed and the associated workload shape the data management. In signal detection it is most important to come to a sound result. For safety issue assessment, the co-operation with partners, especially with the other agencies, but also the access to external experts are most important. Speed was the most relevant factor for decision-making. Finally, in the area of communication and action to protect public health, the speed with which decisions are implemented, the harmonisation of communications and the outcomes of regulatory action are perceived the most relevant critical success factors.

It appeared that besides factors for each phase of pharmacovigilance, a number of general factors are important for the performance of the system. These are the legal framework conditions which the agencies and other stakeholders have to comply with, resources in terms of staff and technical equipment, co-operation and collaboration (which is again related to the respective duties of information exchange etc. made by the legal framework), if pharmacovigilance is integrated into the larger strategy for Public Health, and the quality management within the agencies.

The systematic of success factors was used as the basis to assign the performance indicators (see chapter 6).

Figure 5.1. Systematic of critical success factors



Source: Fraunhofer ISI 2005

6 Performance indicators

The performance indicators were developed on the basis of a draft list derived from the literature as well as from the agency interviews. This list can be found in Table 6.1 below; it was organised in a similar structure as the critical success factors in chapter 5 and was also subjected to a Delphi survey with the advisors as evaluators. They were asked to rate the draft indicators according to the questions

- "**Relevance**: How important is the indicator to obtain a valid picture of the performance of the European System for Pharmacovigilance?"
- "**Practicability**: How easy is it to obtain the data for this indicator?", and
- "**Interpretation**: How easy is it to interpret the results?"

The indicators that were assessed the best by the experts in the three aspects (relevance, practicability, interpretation) are listed in the following table (Table 6.1). The full results of the Delphi survey on performance indicators can be found in Annex 4.

The performance indicators built the backbone of the written agency survey within which data for as many indicators as possible were collected.

Table 6.1. Most important performance indicators

1 Data collection
• Total number of ICSRs from your country received in last year
• Number of ICSRs from your country received in last year from MAHs
• Number of ICSRs from your country received in last year direct from HCPs
• Number of ICSRs from your country received in last year direct from pharmacists
• Number of ICSRs from your country received in last year direct from other HCPs
• Number of cases received/total number of ICSRs from your country
• % of serious ICSRs from your country
• Rating-scale: Usefulness of routine data from your country for safety issue assessment compared to other information (very useful…only marginally useful)
• Rating-scale: Access to all necessary data (very easy…very difficult)
• % of PSURs that comply with E2C
2 Data management
• Number of ICSRs processed
• Rating-scale: Internal cooperation within agency incl. IT staff (very good…very bad)
• Rating-scale: Time between data entry and transmission to EMEA or MAH (adequate … far too slow)
3 Signal detection
• Rating-scale: Information for signal detection (always sufficient…often very incomplete)
• Data sources routinely used for signal detection (routine data, literature, registries…)
• Rating-scale: Available statistical tools for signal detection (always adequate…often very inadequate)
• Rating-scale: Time between detection of signal and reporting (publishing) (adequate … too slow)
• Rating-scale: Work that is done within your country and at the same time in other MS or on EU level (very little…very much)
• Rating-scale: Use of information from other agencies (in nearly all cases…very seldom)

4 Safety issue assessment
• Number of PSURs assessed
• Rating-scale: MAHs compliance with duty to assess safety issues (very good…very bad)
• Rating-scale: Availability of external expertise in your country for routine cases (always when necessary…very scarce)
5 Decision-making
• Rating-scale: Come to adequate decisions (for NAPs/MRPs/CAPs) (always…seldom)
• Rating-scale: Come to decisions in good time (for NAPs/MRPs/CAPs) (always…seldom)
6 Communication/Action
• Rating-scale: Time from 1st signal to action with respect to this safety issue (adequate … too slow)
• Rating-scale: Implement decisions in good time (for NAPs/MRPs/CAPs) (always…seldom)
• Rating-scale: Reaching targets for timing of communications (very good…very bad)
• Number of information events for HCPs with participation of agency
• Number of responses to inquiries by HCPs
• Number of other answered queries
• Number of inspections of MAHs carried out where PhV was an issue (at least partially; including inspections that were carried out by other authorities in the country)
• Rating-scale: Consistency of communication across stakeholders (incl. MAHs) (very good…very bad)
• Number of ICSRs from your country before vs. after communication
• Total reporting rate per million inhabitants in 2004
• Reporting rate in children per million inhabitants in 2004
• Number of market withdrawals of drugs (compared to other countries)
• Number of suspensions of marketing authorisation
• Number of dear doctor letters sent
• Number of changes in SPCs made
• Number of applications for variations adopted/refused
• Incidence of ADR-relevant diseases
• Hospitalisations due to ADR
• Mortality due to ADR
• Number of quality-adjusted life years lost due to ADRs
• Potential years of life lost due to Adverse effects from medicines
• Changes in consumption data
• (Change in) Prescription data (controlled for population parameters)
7 General factors
• Number of staff in full-time-equivalents
• Number of scientists in full-time-equivalents
• Annual budget of the agency
• Number of Regional centres in your country
• Total number of staff (sum of all regional centres) for routine work
• Number of nationally authorised products in your country
• Number of MR authorised products in your country
• Number of centrally authorised products in your country
• Pharmaceutical consumption by drug classes
• Number of documents prepared (legal acts, guidelines)
• Number of scientific publications with at least one author from the agency in last year
• Rating-scale: Compliance of agency with dates/requirements (very good…bad)
• Rating-scale: Meeting general targets for timing (very good…very bad)
• Rating-scale: Compliance of MAHs with 15 days (very bad…very good)
• Rating-scale: Compliance of MAHs with legal requirements (very bad…very good)
• Number of documents sent through EudraNet (RAS, NUIS, others) by sender, concerned MS, issue, channels

• Number of regular meetings with external experts
• Number of irregular consultations with external experts
• % of staff trained per year
• Number of training measures (internal or external) with at least one participant from the agency

Source: Fraunhofer ISI 2005

This set of performance indicators has been carefully developed to cover the relevant areas of the pharmacovigilance system including the critical success factors. However, it also has its shortcomings, the most important of which is that the outcomes of communication and action cannot be adequately measured with the existing data in an economic and valid way. The experiences with the agency survey showed that for the following indicators it was difficult to determine the necessary data:

- Pharmaceutical consumption by drug classes: Data are frequently not available.
- Rating-scale: Usefulness of routine data from your country for safety issue assessment: It was unclear, how the agencies understood the term "usefulness".
- Rating-scale: Information for signal detection sufficient: A comment was that in pharmacovigilance information "is never sufficient", while 6 agencies answered that information had always been sufficient, probably pointing out an unclear understanding of "sufficient information."
- Rating-scale: Work that is done within your country and at the same time in other MS or on EU level: Different opinions seem to exist of what tasks are necessary to be done on the national level and what competences should or can be transferred to central structures.
- Rating-scale: MAHs compliance with duty to assess safety issues: Information from the interviews indicate that the processes at the MAHs are not sufficiently transparent for the agencies, partially because only few inspections are made. Therefore it is questionable if the agencies can validly assess the compliance of the MAHs with signal detection duties.
- The number of responses to inquiries by HCPs, number of other answered queries, and number of documents prepared are often not documented.
- For the impact: The number of ICSRs from your country before vs. after communication often not documented;
- Reporting rates are difficult to interpret because they are input factors for the system but partially also the output of approaches to improve reporting by education of the reporters etc.
- The number of market withdrawals is difficult to interpret because these result from different reasons including internal decisions within the MAHs and causes other than safety concerns.
- Outcomes of action: Missing data on hospitalisations and mortality, QUALYs and life years lost due to ADRs because of lacking prospective studies with such endpoints.

Most of the indicators, however, proved to be practicable and useful to describe the different aspects of the system and come to meaningful results.

7 Case studies

The two case studies were carried out to obtain a deeper understanding of the processes that underlie the detection and assessment of safety signals and how they lead to decisions made.

7.1 Statins case

This safety case provides us with a number of learning points: Firstly, problems like rhabdomyolysis, the extent of which is hard to determine in a pre-clinical setting or from clinical trials, rely heavily on the optimal use of post-marketing approaches, including appropriate use of spontaneous reporting data, record linked databases and the like. With respect of systematic pooling of and signal detection out of spontaneous reports the successful implementation of the EudraVigilance network is essential. Moreover, priority should be given to develop further European pharmacovigilance/pharmacoepidemiology data platforms. In various MS (e.g. UK, Denmark, Portugal, and the Netherlands) significant progress has been made, but more action is needed in order to stay at the cutting edge. The case shows repeatedly the vulnerability of a medicine when inappropriate dosing (directly via a too high dosage form (cerivastatin 0.8 mg) or indirectly via a pharmacokinetic interaction due to co-prescription with fibrates) occurs. Inappropriate dosing has at least two angles: firstly, are we introducing new medicines on the market with clinically the most suitable dose. Two independent studies have revealed data that this is still not the case[13,14]. Moreover, inappropriate dosing as a result from poor prescribing and non-adherence with label directions is a major problem related to drug prescribing and taking behaviour. So far we have little information about what prescribers do with label information and label changes. Moreover, when information is there, the results are not very encouraging[15]. Therefore, effective strategies for risk communication towards prescribers should be a topic that should feature on any agenda of risk management strategies. A typical problem related to the statins is also the fact that dosing-dynamics in this drug class is driven by the dominant paradigm to achieve the strongest cholesterol reduction as fast as possible. This paradigm, supported also by myriad clinical trials, is evidently misused in drug promotion and marketing. How this will impact future drug utilization and safety issues could be a focus of further investigation.

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[13] Cross J, Lee H, Westelinck A, Nelson J, Grudzinskas C, Peck C. Postmarketing drug dosage changes of 499 FDA-approved new molecular entities, 1980-1999. Pharmacoepidemiol Drug Saf 2002; 11: 439-446.

[14] Heerdink ER, Urquhart J, Leufkens HG. Changes in prescribed drug doses after market introduction. Pharmacoepidemiol Drug Saf 2002; 11: 447-453.

[15] Wilkinson JJ, Force RW, Cady PS. Impact of safety warnings on drug utilization: marketplace life span of cisapride and troglitazone. Pharmacotherapy 2004; 24: 978–986.

7.2 SSRI case

In terms of contents this safety case provides us with a number of learning points: Firstly, the nature of the adverse event can have a very high impact on the regulatory process: it is rare; no completed suicides were reported in 4100 children included in trials, and associated with the indication of prescribing[16]. Furthermore, in these types of adverse events it is hard to discern whether there is a class or a single drug effect. Three major limitations that have been identified in the assessment of safety in child and adolescent psychopharmacology can be applied to this case as well[17]:

Considerable inconsistency in the way safety is assessed. Defining the adverse outcome is difficult. Since completed suicides rarely occur in trials, other markers must be used. An example of the problems in definition is the term 'emotional lability' that was used in clinical studies included in the initial submission to the FDA in 2002. Apparently, behind this term lay factors related to the outcome of interest, suicidal behaviour.

Dearth of research. Studies into the topic of suicidal behaviour in children during antidepressant use are still few. To further understand this topic, especially in relation to detecting future problems at an earlier stage, more research is required.

Improved identification of adverse events. In this case the main source of data was clinical trial data. Observational data was only used in a supportive way; spontaneous reporting data did not play a significant role in the regulatory decision process. With regards to the latter improved data-mining techniques and institutionalized follow-up procedures may help to make better use of available research, hopefully leading to better, and earlier, signal detection.

When managing drug safety issues, considering the impact of action taken on patients is of key importance. Abrupt discontinuation is often unwanted and requires monitoring of patients after the announcement of the safety alert. This does not only address warnings issued to HCPs but particularly publicly available information on safety concerns, be it from official bodies, MAHs or unofficial sources. The SSRI case shows that it is not sufficient to inform HCPs about the risks of abrupt changes in the prescription of a drug but that the patients should be prevented from stopping to take the drug after a public warning without consulting their physician. Moreover, especially when a withdrawal affects a significant part of treated patients the impact can be very large. For example, when the CSM advised against the use of most SSRIs in children and adolescents in the UK, it was estimated that half of the antidepressants that were used in this population were of the group that was considered 'unsafe'. The risk for withdrawal reactions has also been described in children[18], and was noted in the 26 April 2005 EMEA press release on the re-

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16 Vitiello B, Swedo S. Antidepressant medication in children. NEJM 2004; 350: 1489-1491.

17 Vitiello B, Riddle MA, Greenhill LL, March JS, Levine J, Schachar RJ, et al. How can we improve the assessment of safety in child and adolescent psychopharmacology? J Am Acad Child Adolesc Psychiatry 2003; 42: 634-641.

18 Diler RS, Avci A. Selective serotonin reuptake inhibitor discontinuation syndrome in children: six case reports. Clin Ther Res 2002; 63: 188-197.

view of antidepressants in adolescents and children[19]. Therefore, effective regulatory management of post-event (e.g. safety restrictions) drug use is warranted.

Great lack of efficacy and safety data of medicines (e.g. SSRIs) in children and adolescents is acknowledged previously but repeatedly received many echoes in this case. In September 2004 the European Commission adopted a proposal for a Regulation of the Council and of the Parliament on Medicinal Products for Paediatric Use (see http://pharmacos.eudra.org/F2/Paediatrics/index.htm), the overall policy objective is to improve the health of the children of Europe by increasing the research, development and authorisation of medicines for use in children. Studies shall be funded that lead to the development and marketing of drugs for children. The long-term follow-up of adverse drug reactions would be an additional requirement for marketing authorisation.

Recently WHO has delivered a relevant review on this topic in the context of the 'Priority Medicines for Europe and the rest of the World'-project[20]. Detailed discussion of this topic falls outside of the scope of this case study, but drug use in children and adolescents will be increasingly prominent in the regulatory environment in the coming years.

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19 EMEA press release 25 April 2005. European Medicines Agency finalises review of antidepressants in children and adolescents. Available from: http://www.emea.eu.int/pdfs/human/ press/pr/ 12891805en.pdf (Accessed 14 September 2005).

20 Zuidgeest MGP, Willemen MJC, Van den Anker JN. Pharmaceuticals and children - Background paper for the Priority medicines for Europe and the world report. Available from: http://mednet3.who.int/prioritymeds/report/background/children.doc (Accessed 14 September 2005).

8 Best practice

Many interesting approaches to solve at least some of the issues that are discussed within the system have been collected from the literature and even more from the interviews with the national agencies. On the national level, some of the problems have been resolved by measures which could partially serve as models for the whole EU system.

8.1 Indicator-based identification of best-practice

8.1.1 Method

In this section we try to identify important differences in critical success factors between countries and possible explanations for them. Hence comparisons are made between the assessment of the critical success factors and indicators for the input and process, like resources or actions. For each phase, only the countries with the best assessment are listed in the tables, as possible examples of "best practice". To get a better overview only a medium-sized set of indicators for the respective phases is presented. Therefore, only indicators with

- a high relevance according to the Delphi survey on performance indicators and
- either some explanatory power or surprisingly little significance – according to our deeper analysis with a more comprehensive set of indicators –

were included. The average value (Median) of all 28 countries plus EMEA (not only for those mentioned in the tables) is given as a comparison according to which the assessment of performance was made. The criterion for good performance was a better-than-average assessment in the "output" variables, the "process" and "input" variables are used to describe which factors might have contributed to this good evaluation.

However, it should be noted that drawing conclusions based on correlations between the indicators is not fully adequate, because a) these correlations cannot be tested statistically due to the small sample size, b) we do only have a tentative understanding of which features can be the causing factors, and c) a large number of different factors (such as different institutional settings) has influence on the performance of the complex system of pharmacovigilance not all of which are known. Moreover, d) not all potentially important factors/outcomes could be measured or can be indicated without impairing the clarity of the presentation. But of course these other factors and additional information e.g. form the agency interviews are used for the interpretation as far as possible.

8.1.2 Data Collection

In the phase of data collection key success factors are the sufficiency and the quality of the information basis. Possible indicators for these characteristics are as-

sessments of the usefulness of routine data and the preparation for a safety crisis by routine data. The ratings found for these items vary in the whole scale range.

In Table 8.1 those countries are listed as examples of good practice, which come off better than the median in one of the two output indicators and are as least as good as the median in the other. E.g., looking at the second column of the table, in the questionnaire the countries were asked how well they had been prepared by routine data for the last crisis on a five-point-rating-scale ranging from 1="very good" to 5="very bad". The median for all countries was the middle value 3, the analogue is true for the assessment how useful the routine data are. Therefore in Table 8.1 all countries are listed which assessed their respective capability with at least "2" in one of these two parameters and at least a "3" in the other. The following columns contain process and input variables that might contribute to the good evaluation of the two output variables.

The following tables are structured in the same way.

While especially larger western countries are quite confident with their data basis, there is much criticism in the self-assessments of some smaller eastern countries (Table 8.1). Most of the confident countries have a quite high amount of data available, e.g. the number of received ICSRs and their reporting rate per sale 2004 mostly lie above the median. However there are some exceptions of well-performing New Member States like Hungary, Estonia or Malta. However, the assessment of the usefulness of the data seems to be lower for countries which have received a very limited number of ICSRs in 2004 which would prevent the statistical analysis of these data on a national basis. High reporting rates as for DE-BFARM, in FR or in NL lead to a very good assessment.

In respect to resources there seems to be no clear connection to the usefulness of the data. This is of course not surprising, but a few countries with high resources even do not obtain a high amount of reports. Countries with a medium-size staff-per-population rate (the whole staff is given in the table including the national plus eventual regional centres in the country) are performing equally well as or even better than countries with extraordinarily high staff, but also a number of agencies with extraordinarily low staff can perform well (e.g. DE-PEI, IT, EMEA). In most of the well-performing larger countries regional centres support the data collection.

Table 8.1: Indicators for Data Collection

	Output Data Usefulness		**Process Data Amount**			**Input Resources**		
	Routine data prep. for crisis	Routine data useful	ICSRs received 2004	Reporting rate total 2004 per sales in US$	Reporting rate total 2004 per million capita	Assess IT-resources	RC performs data coll./ management	PhV-staff[21] NCA+ RC per million capita
BE	3	2	2945	9.26	283.27	3	0	0.8
DE-BFARM	1	3	15750	38.6	190.84	2	1	1.0
DE-PEI	1	1	3376	8.27	40.91	1	1	0.1
EMEA/ EEA-28	2	2	.	.	.	2	.	0.1
EE	2	3	61	.	45.15	3	.	0.7
EI	2	2	1727	6,67	428,78	3	.	.
FR	2	2	20116	35.29	335.82	3	1	1.7
HU	3	2	234	0.79	23.13	2	.	0.3
IT	2	2	6350	13.12	109.69	2	.	0.2
MT	2	2	32	.	80.02	2	.	4.5
NL	1	1	5050	18.3	310.62	2	1	1.8
PT	2	3	1718	5.69	164.01	2	1	1.7
SE	2	2	4124	12.53	459.46	2	1	4.2
MEDIAN all countries	3	3	1491	8.27	152.93	2	1	1.2
rating scale	1 = very good	1 = very useful				1 = totally sufficient	1 = yes	
	5= very bad	5 = marginally useful				5 = very insufficient	0 = no	

Source: Fraunhofer ISI 2005

8.1.3 Data Management

Reliability and speed are the most important goals in the phase of data management. As the former factor can hardly be analyzed with the data from our surveys, the latter shows huge country differences. The assessment time for PSURs varies between one and ninety days across the countries. Surprisingly there is less variation in the subjective assessment of the time for data processing. As already shown

[21] Staff for pharmacovigilance, scientific and administrative.

in chapter 3, the majority of agencies considers the time in which they do this task as adequate. But there are some worrying exceptions in which the time is assessed very negatively (not given in the table). These cannot be explained by the workload alone (absolute numbers of ICSRs or PSURs as well as reporting rates). But in combination with the input indicators it can be concluded, that a lack of human and IT-resources often results in an insufficient duration of the process. As the following Table 8.2 shows, some countries with few resources also provide good results. Listed are countries with process duration self-assessed as rather adequate.

The well-performing countries are here defined as those which assess the time they need for data processing as adequate (value 1) or with a value of 2 and at the same time having assessment times for PSURs of maximally 10 days. These agencies mostly have good IT resources. Having all data under one interface, the number of persons working for this task (not shown in the table), and the involvement of regional centres seem not to influence the time for data processing.

Table 8.2: Indicators for Data Management

	Output Duration of process		**Process Instruments/ Workload**		**Input Resources**	
	Assess time data processing	Duration assess PSURs (days)	All data accessible under one interface	ICSRs received 2004	Assess IT-resources	RC performs data coll./ management
BE	1	,	0	2945	3	0
DE-BFARM	1	20	0	15750	2	1
DE-PEI	1	36	1	3376	1	1
DK	1	3	1	1920	2	,
EE	1	4	,	61	3	,
EI	1	,	0	1727	3	,
ES	1	15	0	7476	2	1
FI	1	,	0	1118	2	,
HU	1	1	0	234	2	,
IC	1	,	0	26	2	,
IT	2	10	1	6350	2	,
NL	1	35	0	5050	2	1
NO	1	30	0	1734	1	1
SE	1	3	1	4124	2	1
UK	1	40	0	20044	1	1
MEDIAN	1	30	0	1491	2	1
rating scale	1 = adequate		1 = yes		1 = totally sufficient	1 = yes
	5= far too slow		0 = no		5 = very insufficient	0 = no

Source: Fraunhofer ISI 2005

8.1.4 Signal detection

The main goal of this phase – to identify all relevant signals – is not adequately measurable. However the analysis of the available data sources, human resources and tools gives some interesting insights.

In the agency questionnaire it was asked which other data – besides ICSRs and PSURs – are or could be used for signal detection or safety issue assessment, including

- routine collection of data or information on post-authorisation safety studies,
- routine collection of data or information on phase IV efficacy trials,
- routine collection of data or information on preclinical studies,
- if and how often sales data are used,
- if the agencies have the capability to link prescription registries with other registries which include health outcomes,

- if the agency initiated or carried out in 2004 ad hoc pharmacoepidemiology studies when a signal needed confirmation or quantification, and
- if the agency initiated or carried out in 2004 pharmacoepidemiological studies for early post-marketing surveillance of new products.

In Table 8.3 countries with availability of at least seven of eight data sources are presented as examples of good practice (the seven data sources in the table below plus information from other authorities which is not presented in the table).

The availability of different data seems to correlate strongly with the country size (none of the small countries met the inclusion criteria for this analysis); small countries seem to lack the access to these "additional" data.

Table 8.3: Indicators for signal detection – Availability of data sources

	Availability of data sources						
	Info PASS collected	Info phase IV studies collected	Info pre-clinical studies collected	Used sales data	Link prescription registries	Studies signal PM surveil.	Studies early PM surveil.
DE-PEI	1	1	1	1	0	1	1
EMEA/ EEA-28	1	1	1	2	0	,	,
FI	1	1	0	2	1	1	,
IT	1	1	1	2	1	1	1
SE	1	1	0	2	1	1	1
UK	1	1	1	2	1	,	,
MEDIAN	1	1	0	2	0	0	0
rating scale	1 = yes	1 = yes	1 = yes	2 = always	1 = yes	1 = yes	1 = yes
	0 = no	0 = no	0 = no	0 = never	0 = no	0 = no	0 = no

Source: Fraunhofer ISI 2005

Table 8.4 shows the minority of countries, which assess their available statistical tools as at least adequate; in respect to statistical tools the majority considers their equipment as (very) inadequate. All of the better-performing have tools for small numbers of cases. Overall there is quite high correlation between these two indicators (assessment of statistical tools and having tools for small numbers of cases) which underlines the importance of statistical tools for small numbers of ICSRs.

Table 8.4: Indicators for signal detection – Analysis tools and resources

	Analysis tools		**Resources**
	Assess avail. statist. tools	Tools for small numbers	RC performs signal detection
EMEA/ EEA-28	2	1	,
DK	2	1	,
NL	2	1	1
UK	1	1	0
MEDIAN	4	0	1
rating scale	1 = always adequate	1 = yes	1 = yes
	5 = often very inadequate	0 = no	0 = no

In the survey it was not distinguished between staff for signal detection and staff for risk assessment

Source: Fraunhofer ISI 2005

Taken the availability and assessment of the analysis tools and the availability of the "additional" data mentioned above together, there are obvious differences especially within the medium-sized countries. Particularly well performing are Finland, Italy, and Sweden, among them Sweden with nearly the highest national staff for pharmacovigilance, but also Italy with relatively low staff resources. It is interesting to note that the well-performing countries in many cases have by far more staff for signal detection (not shown in the table) than they have for data management, probably due to particularly good IT resources that allow shifting staff from the earlier stages of pharmacovigilance to the later.

8.1.5 Safety Issue Assessment

To generate the necessary knowledge for an adequate safety assessment either in-house or external expertise is indispensable. Fortunately a lot of countries state to have good access to both sources of expertise, especially the larger countries. On the other side there are some small and medium-sized countries with serious problems in this issue. Not surprisingly this is reflected on the input side by a small number of staff for risk assessment in these countries (not shown in the table). In addition, small countries mostly state insufficient compliance of MAHs with their duty to assess signals. As can be seen in Table 8.5 there are also some exceptions of medium-sized countries with better conditions, e.g. Norway.

The table includes countries which state that they can identify/assess signals without help and have easy access to external expertise on a routine basis and in exceptional cases as examples of good performance.

Table 8.5: Indicators for safety issue assessment

	Country expertise			MAH compliance	Resources
	Receive support from experts routine	Support from experts exceptional	Identify/ assess signals without help	MAHs comply analysis of signals	RC performs safety issue assessment
BE	2	2	1	3	0
DE-PEI	1	1	1	3	1
DK	1	1	1	2	,
EMEA/EEA-28	2	2	1	2	,
FR	2	1	1	3	1
HU	2	2	1	1	,
IT	2	1	1	2	,
NL	2	2	1	3	1
NO	2	1	1	3	0
SE	2	1	1	2	1
UK	1	1	1	1	0
MEDIAN	2	2	1	3	1
rating scale	1 =very easy	1 =always when necess.	1 = yes	1 = very good	1 = yes
	5 = (nearly) impossible	5 = (nearly) impossible	0 = no	5 = very bad	0 = no

In the survey it was not distinguished between staff for signal detection and staff for risk assessment

Source: Fraunhofer ISI 2005

8.1.6 Decision-Making

As already shown in chapter 3.7.5 the majority of the countries assess the adequacy and duration of the decision-making process as rather positive.

In Table 8.6 only those countries are listed as particularly good performers, which are satisfied in respect to decision-making for NAPs and MRPs. According to the interviews, these countries do not have a common decision process which would have allowed identifying advantageous commonalities, and also the equipment with staff for this task varies a lot between agencies. Therefore it is very difficult to conclude here what leads to this aspect of best practice.

The responses are quite homogeneous for the different types of products within countries: in a number of countries the adequacy of decisions is evaluated negatively be it for decentrally or centrally authorised medicines, in others it is merely positive for both types. The negative evaluation might relate to difficult consultation or even arbitration between MS agencies that is also needed for most decentrally authorised products, to problems regarding regulatory aspects, but also to the general difficulty to decide on the basis of weak signals or other uncertain conditions.

Table 8.6: Indicators for decision making

	Decision Making		
	Adequate decisions found NAPs	Adequate decisions found MRPs	Adequate decisions found CAPs
BE	1	1	1
CY	1	1	1
DE-BFARM	1	1	1
DE-PEI	1	1	3
HU	1	1	1
SE	1	1	1
UK	1	1	1
MEDIAN	2	2	2
rating scale	1 = always	1 = always	1 = always
	5 = seldom	5 = seldom	5 = seldom

Source: Fraunhofer ISI 2005

8.1.7 Communication/Action

Critical factors in the communication with stakeholders are the consistency of communications and actions as well as the speed of implementing them.

In Table 8.7 those countries are presented, which come off better than the median in one output indicator (assessment of the time between signal and decision, consistency of the communication between agencies, or consistency of communications between agencies and MAHs/HCPs), and are at least as good as the median in the other two.

The consistency of the communication between is criticized by a few countries with the main argument that the publication times of safety information is not always coordinated well.

The variation of the assessments is quite high and cannot be explained by the different size or the geography of the countries. The overall correlation between the timeliness and the responsible staff is also quite low. However it should be noted that the countries with the highest staff (in absolute and relative numbers; not shown in the table) are very confident with the speed in this phase, but another strategy seems to exist that concentrates communication/action on only a few members of the staff. According to the interviews often the director of the agency is solely responsible or communication is centralised through a press officer. In nearly half of the countries where regional centres exist they are involved in communication or action.

Table 8.7: Indicators for communication/action

	Output Consistency/speed			**Process Actions**		**Input Resources**
	Assess time signal-decision	Consistent comm. agencies	Consistent communica-tion agencies - MAHs/HCPs	Follow-up the impact	Inspec-tions of MAHs for PhV issue	RC perform communica-tion
BE	2	1	2	0	0	0
DE-PEI	2	1	2	1	,	0
DK	1	2	2	1	8	,
EE	1	2	2	0	,	,
EMEA/EEA-28	2	2	2	0	15	,
GR	3	1	2	0	,	,
PT	2	2	2	0	16	0
UK	1	2	2	1	61	1
MEDIAN	3	2	2	0	0	1
rating scale	1 = ade-quate	1 = very good	1 = very good	1 = yes		1 = yes
	5= far too slow	5 = Very bad	5 = very bad	0 = no		0 = no

Source: Fraunhofer ISI 2005

For the communication between the agencies and HCPs a more detailed analysis is needful. While the differences in the opinions about the cooperation with HCPs are only small, the assessment of the influence on prescription behaviour differs largely. As Table 8.8 shows, this does not seem to be country-size specific or to correlate with human resources (not shown in the table). All countries with output ratings at least on the median are presented. The influence on the prescription be-haviour is in general only assessed as moderate.

Table 8.8: Indicators for communication/action with HCPs

	Output Influence/ Cooperation		**Input Resources**
	Influence on prescription behaviour	Cooperation with HCPs	RC perform communication
DE-PEI	3	2	0
DK	2	2	,
EE	2	2	,
EI	2	2	.
GR	2	1	.
IC	3	2	.
NO	2	2	0
PT	3	2	0
SE	2	2	1
MEDIAN	3	2	1
rating scale	1 = very good	1 = very good	1 = yes
	5 = very weak	5 = very bad	0 = no

Source: Fraunhofer ISI 2005

Another explanation for the weak influence of communications or actions could lie in the amount of actions or in the usage of certain communication channels. Most countries provide general and specific information to different groups of HCPs. But it is conspicuous that this does not apply for some countries with negative assessments for the above output indicators for communication/action, which seem not to use all available channels. In the respective Table 8.9 the same countries as above are listed, that is they assess the influence on the prescription behaviour as well as the co-operation with HCPs to at least moderately good (value 3).

Table 8.9: Indicators for information provided to HCPs

	Communication General Infos to Stakeholders					**Communication Specific Infos to Stakeholders**				
	General info Individual doctors	General info Medical associations	General info Professional journals	General info Pharmacists	General info Other HCPs	Specific info Individual doctors	Specific info Medical associations	Specific info Professs journals	Specific info Pharmacists	Specific info Other HCPs
DE-PEI	1	1	1	1	1	1	1	,	1	0
DK	,	1	1	1	1	,	1	1	1	1
EE	1	1	1	1	1	1	1	1	1	1
EI	1	,	,	,	1	1	1	1	1	1
GR	1	1	0	1	0	1	1	0	1	0
IC	1	0	1	1	0	1	0	1	1	0
NO	1	0	1	1	0	1	0	1	1	0
PT	1	1	1	1	1	1	1	1	1	1
SE	1	1	1	1	1	1	1	1	1	1
MEDIAN	1	1	0	1	0	1	1	1	1	1
rating scale	1 = yes	1 = yes	1 = yes	1 = yes	1 = yes	1 = yes	1 = yes	1 = yes	1 = yes	1 = yes
	0 = no	0 = no	0 = no	0 = no	0 = no	0 = no	0 = no	0 = no	0 = no	0 = no

Source: Fraunhofer ISI 2005

8.1.8 General aspects

Overall some cautious conclusions can be drawn from this analysis which concern the pharmacovigilance process as a whole:

- The correlation between the human resources and indicators for outcome is for some phases rather low. This counts especially for relative indicators like the combined PhV-staff of NCA+RC per capita. Also if other overlapping explanations like geography are kept in mind, it is hardly possible to identify causal connections between resources and outcomes. However, the better performers generally have a certain minimum of staff and assess their IT resources as more positive than the agencies do that perform less well.
- Some countries are performing well in almost all phases and therefore are frequently presented in the tables above as examples for best practice. However it is not easy to determine the causes for this overall good performance as it is certainly impossible to evaluate all critical success factors together and because most output indicators are subjective ratings. In addition, external conditions have a high impact on the performance of the agencies within the whole system of pharmacovigilance as are e.g. the agency's budget, compliance of MAHs etc.
- Regional centres seem to be a very helpful support for the work of the national centres especially in data collection and communication. The regional centres assist the national agencies particularly in the first phases, so that

the latter are able to concentrate more on tasks like signal detection and safety issue assessment. The output indicators show some success signals for this strategy. The positive appreciation of regional centres is confirmed in the interviews with the corresponding countries.

8.2 Results from the interviews

This section identifies "best practice" from strong points in the national systems that were identified on the basis of the interview partners' statements. Because of the large quantity and diversity of the approaches in the NCAs the presentation cannot be complete. Again, the selection of these results depends on the evaluation by the evaluators of their relevance for the critical success factors. The results are organised according to the phases or pharmacovigilance and respective critical success factors.

8.2.1 General factors

8.2.1.1 Legal framework conditions

Germany has good experiences with the implementation of the law in the form of a stepwise procedure including risk assessment, decision-making and communication. Other examples of supporting national legal frameworks are Slovenia and Lithuania where the new harmonized legislation and the main points of Pharmacovigilance are explicitly mentioned in the law. Spain has a legal obligation of HCPs to report ADRs which cannot be controlled but is assessed as good to have, although not sufficient, because it at least shows that PhV is an important issue.

In Italy for reimbursement of new drugs nearly always the conduction of a PASS or other monitoring measure is required, prescription can be limited by issuing so-called "AIFA-notes".

8.2.1.2 Sufficient number of staff

The Irish Medicines Board has set up a detailed plan on how much personnel are needed for the different work steps from which other countries could learn.

8.2.1.3 Expertise

A number of agencies stress the importance of their long and good collaboration with the WHO-UMC in submitting to and using the database of ICSRs for signal detection as well as participating in training measures there.

The Cypriot agency has easy access to external experts through a system of governmental HCPs.

The German PEI made positive experiences with ad-hoc expert groups at which practitioners are easily won to participate. A standing committee of the Drugs commission of the German physicians' association is also often a helpful partner.

In the Czech system, HCPs are traditionally used to provide data/statistics and therefore has – compared to other smaller countries – relatively high reporting rates.

8.2.1.4 Technical resources

Some of the agencies made high investments in new IT infrastructure, as e.g. the UK, Ireland, Cyprus, Germany-BfArM, partially already in preparation of future requirements regarding the planned data warehouse.

8.2.1.5 Co-operation

Co-operation with regional centres for pharmacovigilance is well-established e.g. in France, where different meetings/workshops with MAH on PhV in the regional centres. A monthly meeting of AfSSAP with the RCs called "technical committee" is held to review reports, signals, and publications.

The decentralized system has increased number and quality of reports and generally the contact to HCPs in Spain and in the UK. As in France, regular meetings on technical questions are held 4 to 5 times p.a. with all Spanish RCs. A safety committee on human medicines exists consisting to one half of members nominated by RCs and the other half by the national agency.

The regional organisation is also well-established in Sweden, good collaboration exists between the agency in Luxemburg and the regional centre in Nancy/France.

Without having regional centres, the external clinicians working together with the NCA in a pharmacovigilance committee are also used to promote reporting in their hospitals in Slovakia.

The co-operation structures within the national agencies differ from country to country. A close collaboration of PhV with the department that registers drugs is assessed as helpful in Hungary. Separate department for pharmacovigilance and marketing authorisation are stressed by the Belgian and other agencies, whereas in Ireland pre- and postmarketing departments are dissolved to allow closer collaboration in shared units or working groups. It is appreciated to have the staff for human, veterinarian medicines and devices in the same agency, and small countries can have advantages in easy formal and informal collaboration with experts and other institutions.

In Sweden a preauthorisation-evaluation exists for the preauthorisation-planning under inclusion of the PhV-department.

The Polish agency will support the interdepartmental exchange of information with a software tool used by the whole agency.

8.2.1.6 Collaboration with stakeholders

The Finnish agency assesses its contacts to the HCPs as particularly good; PhV and the agency in general have a good reputation in the media, they are trusted by all parties. The same is true for Ireland where extensive contacts are nurtured with the MAHs and industry associations. Comprehensive discussions with MAHs are described by the German PEI.

Cyprus and the Czech Republic can draw on good collaboration with Medical Services and medical societies as a whole that are approached as multipliers; actions (e.g. contraindications) are discussed with practitioners which results in good feedback on factors that might otherwise have been underrepresented, e.g. costs of different forms of application, reimbursement, distribution conditions, health insur-

ance companies. Contact to medical societies can improve the influence on clinical guidelines and thus probably on the prescription behaviour

8.2.2 Data collection

8.2.2.1 Have sufficient data

The German PEI and the Italian agency can initiate additional post-authorisation safety studies. In the Czech republic a database similar to UK GPRD, namely a voluntary registry of medical records is available, as are health statistics, data from vaccination programmes, on abuse of drugs etc.

In other interviews, the registry system of Sweden and a large amount of epidemiological data in Spain were underlined.

8.2.2.2 Quality of data

In Denmark the provisions of "Volume 9" on PSURs have been translated into a national guidance, after that the quality of PSURs improved.

Seminars on pharmacovigilance and regulatory activities for practitioners are offered in several countries, e.g. in Italy where credit points for continuous medical education can achieved this way; in Germany seminars on ADRs of vaccination are offered.

8.2.3 Signal detection

8.2.3.1 Soundness

Sweden has specific data mining tools for signal detection.

8.2.4 Decision-making

Decisions in Poland are sometimes faster than on EU-level, and decisions in Spain are made by a committee that is independent from the committee that decides on MAs.

8.2.5 Communication and action to protect public health

8.2.5.1 Speed of implementation

Sweden has provisions for particularly fast action.

8.2.5.2 Harmonisation of communications

The Danish agency has recently changed its departmental structure to improve the transparency and improve information for the public.

Poland publishes all SPCs on the internet. The internet is also used in Finland to automatically forward PhV-information to the website of the Finnish Medical Soci-

ety, and Sweden – as other agencies – can use the agency's press office for pharmacovigilance issues.

9 Discussion of strengths and weaknesses of the European system of pharmacovigilance

The following strengths and weaknesses of the system summarize the results of the empirical studies above. Additional items are selected from the respective question in the agency interviews in order to represent the perspective of these "internal experts" as far as possible. However, the project team was fully responsible for the appraisal of all the results and for the selection of the points that are emphasized in the following paragraphs. The order of the strengths and weaknesses is again according to the phases of pharmacovigilance and respective critical success factors plus an advancing paragraph on general factors.

9.1 General factors

9.1.1 Legal framework conditions

The strengths and weaknesses of the European PhV System relating to the regulatory system can be summarised as follows:

Strengths of the PhV System	Weaknesses of the PhV System
• The system harmonises regulation, pharmacovigilance practice, product information, communication and action across MS. • International co-ordination leads to stronger power of regular action. • The system for CAPs is straightforward, rapid, rational and comes to binding decisions. • The system will allow Pharmacovigilance Planning (E2E) incl. a more proactive approach by agencies and MAHs.	• The system is complicated and difficult to understand (many responsible authorities; different procedures and responsibilities for MRPs; NAPs; CAPs)[22]. • The system is very difficult to overlook despite the existence of detailed guidances. This makes it difficult to find out the steps to do in a particular situation especially for smaller agencies with less specialized staff for regulatory affairs. • Different implementation is caused by e.g. diverging health systems in the MS. • Existing instruments are not fully applied, especially in the control of the MAHs' compliance with requirements. Not all agencies have all guidances for all phases of pharmacovigilance in place. • The use of assessment reports from other countries sometimes ham-

[22] See also Bendall 2004.

Strengths of the PhV System	Weaknesses of the PhV System
	pered by confidentiality issues. • The integration of the new MS is still problematic and impairs the full functioning of the whole system; new MS are not yet able to fully contribute to the PhVWP. • Different opinions with respect to which minimum of information/discussion is necessary at national level. • The collaboration of CHMP with PhVWP is assessed by a number of agency representatives as suboptimal (e.g. parallel/duplicate work, uncoordinated decisions). • Long-lasting discussions take place. • The cooperation with academia is weak (causes: confidentiality of data; lack of funding). • The weight on the system for spontaneous reports is too strong despite the high relevance of studies in recent crises. Some stakeholders doubt that the new legislation including the Clinical Trials Directive offer sufficient means to yield the necessary prospective safety studies.

The analysis has shown that the current European System of Pharmacovigilance has achieved an advanced state of development. If implemented reasonably, from November 2005 onwards the recent reform will give the authorities additional tools, as well as greater scope for urgent regulatory action, increase transparency on safety issues and facilitate communication. Moreover, it will allow a more proactive approach to pharmacovigilance.

9.1.2 Sufficient number of staff

With respect to the number of staff available, the strengths and weaknesses of the European PhV System are the following:

Strengths of the PhV System	Weaknesses of the PhV System
• There are agencies which have – according to their self-assessment – sufficient staff for their pharmacovigilance tasks, a number of agencies have made calculations how much staff they need to comply with the requirements. Other agencies can use this as an argument to request at least a minimum of staff for themselves.	• Low budgets are available for pharmacovigilance in some agencies. This hampers the number of available staff (partially because well-educated staff cannot be won with the salaries that the agencies can pay). • Staff of some agencies seems to lie under a certain minimum of required staff.

The number of staff varies tremendously across agencies. Sufficient staff is a key factor for quality and velocity of the work. Sufficient resources are needed in the MS to reach comparable staff numbers relative to their population sizes.

9.1.3 Expertise

Strengths and weaknesses of the European PhV System in terms of expertise can be summarised as follows:

Strengths of the PhV System	Weaknesses of the PhV System
• The system encourages support from other MS and provides opportunity to learn from other agencies' experience. • Expertise is combined, a forum exists for discussion of scientific and practical issues; peer review is provided. • Expertise, assessments and other documents developed on EU level can be used by the other agencies.	• The capability for safety issue assessment does not exist in all agencies. • According to the complex system and lack of experienced staff, some of the agencies would need more support to be enabled to comply with the requirements. • Training within the system is partially assessed by MS as insufficient and expensive. • The use of assessment reports, SOPs and other documents is not always optimal. • For some agencies it is difficult to hire well-educated staff because there is too few in the country and because they cannot pay competitive salaries. • For some agencies difficulties exist to find external experts (e.g. pharmacoepidemiologists).

Concerning the training in handling pharmacovigilance issues and the whole system some MS refer to good offers of other institutions, e.g. the WHO-UMC.

9.1.4 Technical resources

The strengths and weaknesses of the European PhV System as far as technical resources are concerned can be summarised as follows:

Strengths of the PhV System	Weaknesses of the PhV System
• The system allows the centralisation of database management and signal detection at the EMEA • Some of the MS agencies have already made large investments into their national databases and abilities to exchange data with EudraVigilance. • The technical resources are generally assessed as good and sufficient with respect to the national situation (e.g. having only a few ICSRs to process annually).	• Some agencies still have communication problems which could in the worst case lead to severe delays in the reaction on public health problems. • Despite EudraVigilance, MS still need large investments into their own database systems; some of the MS agencies seem not to have adequate resources for this. • MS agencies develop own database solutions with little use of EMEA's, other MSs' or third parties' experience, this reminds somehow to inventing the wheel a second time.

9.1.5 Co-operation

The strengths and weaknesses of the European PhV System regarding the co-operation between the agencies can be summarised as follows:

Strengths of the PhV System	Weaknesses of the PhV System
• The share of work is good if MS comply with their roles (e.g. active rapporteurs). • Information can be exchanged rapidly, agencies are generally notified quickly of safety issues. • The system allows good access to information from other MS (esp. relevant for small MS). • EMEA gives good backing for MSs' decisions and arguments for their implementation.	• Lots of discussions are necessary to represent all MSs' needs. • Being dependent on other agencies e.g. as a concerned MS is a problem as long as the agencies' work is of different quality. • Different opinions exist what amount of work should be done at the national level, leading to different assessments of necessary and unnecessary duplication of work, which is assessed by some of the agencies as relatively high. • Some agencies do a larger share of work for the community than others. • Communication between MS agencies and EMEA is sometimes assessed as difficult.

Some interview partners in the agencies criticised the communication of the MS agencies with the und EMEA to some extent. Co-ordination is said to be missing if the EMEA negotiates with a large company's headquarters and the MS with the subsidiaries in their own country. In addition, as it was the case for Coxibes, EMEA sometimes reacts too fast and then has to send updated information to the agencies.

The completion of some of EMEA's projects (as E2E) is seen as unrealistic.

9.1.6 PhV embedded in larger Public Health strategy

The strengths and weaknesses of the European PhV System can be summarised as follows:

Strengths of the PhV System	Weaknesses of the PhV System
• Some agencies have integrated pharmacovigilance into a broader understanding of drug or even general consumer safety including e.g. the protection against counterfeit medicines.	• For some agencies the political support is weak, as pharmacovigilance is not perceived by the public as important issue of public health. • According to some interview partners, the public and even HCPs do frequently not understand that medicines normally do have side effects and instead of absolute safety the balance of risk to benefits has to be optimised.

9.1.7 Collaboration with stakeholders

The strengths and weaknesses of the European PhV System can be summarised as follows:

Strengths of the PhV System	Weaknesses of the PhV System
• There are different strategies of how agencies communicate with HCPs that can be used as models of best practice. • The new legislation offers stronger instruments to request information or studies from MAHs and enforce compliance by penalties.	• The agencies' influence on the prescription behaviour is weak. • The MAHs' compliance e.g. with the submission of PSURs as well as the implementation of regulatory action is often not checked and sometimes seems suboptimal. • The assessment of safety issues and decision-making process in the MAHs is sometimes unclear and leads to unforeseeable results. • Responsibilities of the agencies for covering internationally active MAHs with headquarters and subsidiaries in different MS are unclear.

9.1.8 General quality management

The strengths and weaknesses of the European PhV System can be summarised as follows:

Strengths of the PhV System	Weaknesses of the PhV System
•	• A systematic quality management is not implemented in the most PhV departments. The regulatory system does not provide clear goals or provisions in this respect. • The agencies have not always met their own internally set targets for compliance with requirements. • If implemented, nearly all agencies state that their audit procedures do not adequately ensure the quality of their work. • The impact of communications is only followed-up on a routine basis by four of the 29 agencies.

9.2 Data collection

9.2.1 Have sufficient data

The strengths and weaknesses of the European PhV System can be summarised as follows:

Strengths of the PhV System	Weaknesses of the PhV System
• The system combines the ICSRs from a large population in order to increase statistical power with which signals can be detected; especially small countries with few reports benefit from this. • Most of the agencies where reporting is mandatory for HCPs find this helpful to improve reporting; some other agencies would welcome mandatory reporting in their country.	• The safety issues can differ from country to country especially because of varying consumption patterns; these differences are often not totally known because of a lack of adequate and comparable data and therefore not always adequately taken into account. • The reporting rates differ greatly between countries. • The agencies are not very well prepared for crises by routine data (ICSRs and PSURs), their usefulness is restricted. Besides ICSR and PSURs data especially on the

Strengths of the PhV System	Weaknesses of the PhV System
	consumption of drugs, but also relevant registries (vaccines, intoxication, drug misuse…), are perceived as highly relevant, but not available and not used sufficiently. • PASSs and other data that can supplement the routine data (ICSRs and PSURs) have played a decisive role in the last safety crises. However, only very few prospective safety studies were prepared in the last years, and some of them have not been independent from the producer of the drug under study. The funding of necessary studies is often not guaranteed. • Except for outpatient care and intrauterine drug exposure, registries that combine drug exposure and outcomes data including ADRs exist in most of the countries. However, most agencies do only have access to these data in exceptional cases, and they are quite infrequently used. • Research into the safety of drugs for children is disparately missing. • A database on products on the market is also missing. • The collection and analysis of PSURs is problematic: A small number of agencies have not even received a single PSUR in 2004 which is an indicator of non-compliance of MAHs; compliance can often not be checked; others get far more PSURs than they can analyse. • The necessities and requirements regarding the collection and review of ADRs and SUSARs from 3rd countries are unclear and may lead to unnecessary duplication. • Even the collection and analysis of PSURs for NAPs results in duplica-

Strengths of the PhV System	Weaknesses of the PhV System
	tion of work, as many of these products are registered also in other MS. • Too little information (ICSRs, studies etc.) is available on herbal/homeopathic products.

9.2.2 Quality of data

The strengths and weaknesses of the European PhV System regarding the quality of the data collected can be summarised as follows:

Strengths of the PhV System	Weaknesses of the PhV System
• Strategies exist and are generally applied to ensure the quality of ICSRs.	• The compliance of MAHs with expedited reporting is routinely checked in only 41% of the cases, the compliance regarding PSURs in only 56%. This impairs the comprehensiveness and representativeness of the data. • PSURs do often not contain much information, e.g. generics PSURS do not include information on the original product.

9.3 Data management

9.3.1 Soundness (Reliability)

Regarding the soundness of data management, the strengths and weaknesses of the European PhV System can be summarised as follows:

Strengths of the PhV System	Weaknesses of the PhV System
• SOPs exist for data management that are generally applied.	• A lot of different IT solutions are used with a wide range of specifity for the necessities of pharmacovigilance.

9.3.2 Speed

The strengths and weaknesses of the European PhV System concerning the speed of data handling can be summarised as follows:

Strengths of the PhV System	Weaknesses of the PhV System
•	• Some duplication of work related to the handling of the same data (ICSRs, PSURs) exists at different

Strengths of the PhV System	Weaknesses of the PhV System
	agencies, especially at the EMEA on the one side and national agencies on the other. • In some agencies, the necessary IT resources for the timely management of the data are not available.

9.3.3 Workload

The workload related to data management has the following strengths and weaknesses:

Strengths of the PhV System	Weaknesses of the PhV System
• The system allows for a systematic share of work between the involved stakeholders (MAHs vs. agencies as well as between different agencies).	• The issue of duplication of work (what is necessary, what is unnecessary duplication?) is assessed heterogeneously by the agencies; some duplication seems to exist at least with reports from 3rd countries and with PSURs. • Duplication of work results from two international systems existing in parallel (i.e. EudraVigilance and the WHO-UMC). Although these systems do partially have different tasks and scopes, as well as different regional coverage, this results in a serious waste of resources.

9.4 Signal detection

9.4.1 Soundness

The strengths and weaknesses of the European PhV System with respect to signal detection can be summarised as follows:

Strengths of the PhV System	Weaknesses of the PhV System
• EudraVigilance and the related procedures build the basis for the effective systematic pooling of and signal detection out of spontaneous reports.	• The success of the combination of expertise and resources for signal detection depends on the full implementation of the provisions; with regard to other areas and dependence on national resources and priorities, this cannot be assumed as guaranteed.

Strengths of the PhV System	Weaknesses of the PhV System
	• As the last crises have showed, other sources of information than spontaneous reports are of outstanding importance for signal detection, which are at the moment still underdeveloped. • Some agencies assess their tools for signal detection as insufficient, especially the tools for small numbers of cases. The case studies showed that improved-data mining techniques and better European pharmacovigilance/ pharmacoepidemiology data platforms are needed for Europe to stay at the cutting edge. • As for data management, it does not seem that the best use is made of work that is mutually done by the European system and the WHO-UMC. • As it can hardly be controlled, the compliance of MAHs in their role to do first-line signal detection is unclear.

9.5 Safety issue assessment

9.5.1 Co-operation

Regarding safety issue assessment, the strengths and weaknesses of the European PhV System can be summarised as follows:

Strengths of the PhV System	Weaknesses of the PhV System
• The system allows sharing work and using assessment reports from other countries. • Opinions given by the CHMP are mostly assessed to have good quality. • Assessments are found by agreement and therefore few discussions are necessary in the later stages.	• The concerned MS depend on the quality of assessment reports that the rapporteurs of RMS agencies produce. • The contributions of the NCAs to the EEA PhV system in terms of assessments carried out are of high variability. Some agencies admit that they do not have the ability to manage safety issues adequately on their own.

Strengths of the PhV System	Weaknesses of the PhV System
	• For some assessments, the agencies find that the pharmacovigilance expertise of the CHMP or the rapporteur's agency was not always sufficient, and that external expertise has not always been used adequately.

Co-operation within the agency/unit as well as external division of labour (experts, committees, other agencies) are especially important for safety issue assessment.

9.5.2 Access to external experts

The strengths and weaknesses of the European PhV System for the critical success factor "Access to external experts" can be summarised as follows:

Strengths of the PhV System	Weaknesses of the PhV System
• The system encourages the use of external experts as for specific safety issues no agency can keep all necessary expertise in-house.	• The quick and reliable access to external experts is a key factor for the speed and often the quality of the assessment. This is not assured for all agencies. Not all MS agencies have the access to external experts when they would need it. • In smaller MS it is unrealistic to find experts for all possible safety issues within the country.

9.6 Decision-making

9.6.1 Speed

The strengths and weaknesses of the European PhV System regarding decision-making can be summarised as follows:

Strengths of the PhV System	Weaknesses of the PhV System
•	• Decisions often need too much time which is partially attributed to complicated structures within the CHMP and between CHMP and the Commission, especially in the case of referrals.

9.7 Communication and action to protect public health

9.7.1 Speed of implementation

The strengths and weaknesses of the European PhV System concerning the speed with which decisions are implemented into communication and action can be summarised as follows:

Strengths of the PhV System	Weaknesses of the PhV System
• The system provides the structures to come to timely actions.	• The time between the detection of a signal and action (reporting/ publishing of the decision) was too long in some cases.

9.7.2 Harmonisation of communications

With regard to the Harmonisation of communications, the strengths and weaknesses of the European PhV System can be summarised as follows:

Strengths of the PhV System	Weaknesses of the PhV System
• The existing procedures communication channels allow harmonised communications in the end in those cases where satisfactory agreement has been obtained between the agencies and when sufficient time is available.	• In some cases MS agencies found that their particular situation (e.g. regarding epidemiology) was not adequately represented in CHMP opinions or Commission decisions. Therefore the implementation of decisions was sometimes difficult. • Regulatory transparency is very important. In the SSRI case it was not possible to uncover the exact considerations leading to the EMEA regulatory decisions (contrasting with the US FDA). • The agencies have only weak means to influence the timing and content of communications (e.g. changes for SPCs) that the MAHs make. • The information for patients e.g. in patient information leaflets is not always harmonised, e.g. if information on generic products is given on the level of the product and not on the level of the active ingredient concerned.

9.7.3 Outcomes of regulatory action

The strengths and weaknesses of the European PhV System regarding the outcomes of regulatory action can be summarised as follows:

Strengths of the PhV System	Weaknesses of the PhV System
•	• The outcomes of regulatory action are only assessed in exceptional cases. • There is very little information about what prescribers do with label information and label changes. Moreover, when information is there, the results are not very encouraging. • The missing information on outcomes is partially attributed to far too few inspections of MAHs with a pharmacovigilance focus.

Generally, the outcomes of regulatory action cannot easily be evaluated, because even the agencies do normally not have such information. Actions are not evaluated pro-actively, and even if changes in the morbidity and mortality caused by ADRs were detected they could not causally be related to single regulatory acts.

10 Recommendations

According to the original project plan, recommendations for making the European Community system of pharmacovigilance more robust were deducted based on task 6 and discussed in the expert workshop. Draft recommendations were derived basically from the literature review and the interviews and were discussed at the expert workshop on June 15.

The recommendations are organised according to the main processes and respective success factors.

10.1 General factors

10.1.1 Legal framework conditions

- To make best use of the existing legal framework, all existing legal rules should be implemented fully and this should be more strongly supervised.
- The impact of the new legislation especially as far as the improvement on the side of prospective safety studies is concerned should be assessed critically after a certain time; if necessary the respective instruments must be sharpened further.
- It should be ensured that all stakeholders including the agencies are aware of their obligations, e.g. that they have all necessary guidelines in place and that they possess all necessary capabilities.
- To improve the clarity and simplicity of the guidelines in order to make it easier to find out the steps to do in a particular situation especially for agencies with less specialized staff for regulatory affairs, a new version of a decision-tree-shaped, probably HTML-based "super-guidance" (like Volume 9) might help to easier navigate through decisions and help to comply with the regulatory requirements.

10.1.2 Sufficient number of staff

- It should be ensured that the agencies have sufficient staff to guarantee the compliance with the requirements concerning legal framework as well as public health. Among these is that at least one qualified person should be available 24h a day and all days of the year to react in safety crises.
- Taken the average of staff as a measure that is available in the agencies, a value of 1.2 full-time-equivalents (FTEs) per Million inhabitants should be attained for pharmacovigilance staff (scientific and administrative personnel together) taken the national agencies and – if available – regional centres that do a part of the legally required work together.
- To support this, PhV should be included into the university education which would increase the pool of well-prepared potential staff members. Political support has to be developed to increase financial resources to pay adequate salaries in order to hold well-educated personnel in the agencies.

10.1.3 Expertise

- The staff has to be aware of its responsibilities. This has to be ensured by sufficient training for new and older staff members on upcoming scientific issues and new regulation.
- According to their responsibilities for the safe use of drugs in their home countries, at least one senior pharmacovigilance expert should be available in all agencies all the time including times of vacation etc.
- Expertise from other agencies should be used as far as possible. The adoption of SOPs or other guidelines that were developed by other agencies would make the other agencies' knowledge explicit and available for one's own work. The same is true for other agencies' assessment reports which are at the moment not systematically used.
- Central structures are necessary to supplement expertise that is missing in one country by persons from other countries or from the EMEA.

10.1.4 Technical resources

- The severe communication problems that some agencies still have must urgently be resolved in the concerned agencies.
- A standard should be defined including not only hardware to manage ICSRs and to run Eudravigilance, but also all other communication technology as (mobile) telephone systems with relay function, ensuring that e-mails are read and answered in due time etc.
- With the development of database systems etc. the agencies should draw as much as possible on pre-existing experience in other agencies and even abroad.

10.1.5 Co-operation

- One senior pharmacovigilance staff in each agency should be reachable 24h a day. This would also improve the agency's co-operation with other agencies, MAHs and other stakeholders in the case of a crisis.
- Within the agency, structures should ensure horizontal collaboration (e.g. with the pre-marketing units and the inspections department/agency).
- More effective structures are needed for the agencies to collaborate with other (national and EU) governmental bodies e.g. in decision-making.
- However, the definition of responsibilities and roles between the EU Member States and EMEA (e.g. in Signal Detection) are not clear for all actors in the agencies. This should be resolved by clear and simple guidelines.
- The division of labour should be as strong as possible. The diverging opinions on what kind and amount of work is necessary at the national level should be discussed and a solution should be found.
- A lot of time and money could be saved if competences were used that exist outside the EEA system. One approach might be "Centres for excellence" for specific tasks (e.g. development of databases or drug classes).

All materials, working papers, draft communications, web-sites, SOPs, blueprints of databases etc. should be made available and used.

- For the sake of homogeneity and fairness, all agencies should contribute to the common tasks according to the size of their population. Less well informed and equipped agencies should be enabled to catch up by practical guidelines and direct support.
- It should be accepted that some tasks are as consuming for small as for large countries and that agencies with fewer own spontaneous reports have other information needs than those with sufficient national ICSRs.

10.1.6 PhV embedded in larger Public Health strategy

- One approach to educate the public, HCPs and policy-makers about the tasks and necessities of pharmacovigilance would be to perceive PhV as one part of a larger health & consumer safety strategy, e.g. by integrating PhV in a system with other "vigilances".
- In public communications and education of HCPs not the absolute safety of drugs, but risk/benefit should be emphasized.

10.1.7 Collaboration with stakeholders

- Agencies should improve their communication with HCPs. Good experiences exist with regular contacts with professional associations etc.
- It is necessary to increase the influence on prescription behaviour. To this aim it is necessary to influence clinical guidelines and Patient Information Leaflets, not only SPCs, according to new evidence. Safety information should be included into HCPs' day-to-day information (formulary…).
- Reporters should be educated and feedback for reporters optimised.
- The collaboration of agencies with MAHs in their decision-making should be improved.
- The MAHs' compliance e.g. with the submission of PSURs as well as the implementation of regulatory action should generally be better controlled. The enforcement of compliance by penalties should be strengthened.
- The existing possibility to request additional surveillance studies from the MAHs has been used only seldom in the past. This can be combined with a conditional or otherwise restricted marketing authorisation for the drug in question. It has to be ensured that necessary studies are carried out.
- The special interests of patients as regards pharmacovigilance must not be neglected at any rate. Patients can contribute a unique perspective on safety issues. Tendencies exist in some agencies to make better use of direct and regular contacts to patients or patients' organisations, this should be extended to all agencies. One approach is to allow patient reporting with validation of the report by a HCP.

10.1.8 General quality management

- A general quality management system should be implemented including the monitoring of agencies' compliance with requirements, regular assessment of relevant indicators, internal audits, learning from practice (Continuous quality improvement) and elimination of weaknesses.
- The outcomes of regulatory action in terms of prescription/use data should be reviewed in important cases.
- The agencies should continue to mutually support themselves in compliance; this will reduce their own workload in the long run.

10.2 Data collection

10.2.1 Have sufficient data

- To improve the access to ICSRs, well-tried multi-channel technologies exist in some member states to improve spontaneous reporting should be applied in all countries. To introduce regional PhV centres in medium-size or larger MS is one of the promising approaches. More education on pharmacovigilance for HCPs could also increase the understanding of reporting and thus improve the reporting rates. The introduction of a legal duty to report should be considered.
- The access to necessary data should be facilitated. Besides ICSR and PSURs data especially on the consumption of drugs, but also relevant registries (vaccines, intoxication, drug misuse…), are perceived as highly relevant.
- A core set of data that complement spontaneous reporting and PSURs should be defined, and where missing, the necessary structures should be created. Priority should be given to develop further European pharmacovigilance/pharmacoepidemiology data platforms.
- The access to premarketing information (including preclinical data as well as the results of clinical trials) as well as to post-authorisation surveillance studies (PASSs) and to relevant scientific literature has to be optimised.
- These data should be regularly used in safety issue assessment.
- To increase the efficiency of collection of ICSRs it should be distinguished between new and other drugs for which particular attention is necessary on the one hand, and "old" and well-known drugs similar to the different frequencies for PSURs over the years after marketing authorisation. The UK black triangle symbol seems to be helpful in directing the HCPs attention to reporting of ADRs.
- The smaller countries rely heavily on international data/information to which they should have best access. This will be realised for ICSRs via Eudravigilance, but should be extended to other resources too.
- The pharmacovigilance planning tools should be used to systematically generate studies in which ADRs are explicitly regarded as endpoints. A scheme to identify priority areas (types of ADRs, classes of drugs) where

studies are of particular need has to be developed, and companies or public sponsors urged to carry out these studies at an adequate level of quality. This might be supported by an international institution.

- The lack of research into safety in children is tackled by the new Commission initiative. It should be checked in due time if it reaches its aims.
- Information on unpublished trials should regularly be included in PSURs. Clinical trial registries and regulatory action should address this problem as it has been recommended frequently in the scientific literature.

10.2.2 Quality of data

- The quality of ICSRs is of outstanding importance. The respective guidelines should be applied. Serious and unexpected paper reports/electronic reports should be validated before adding them to database.
- At least serious/unexpected reports and fatal cases should be followed-up to receive all available data on the case. This is also a measure to inform the reporter that her/his report was well recognized.
- Education of reporters to support the quality of reports should be practiced wherever possible.
- PSURs and all other data received should be routinely checked for timeliness and quality; this should be supported by PhV inspections at MAHs.

10.3 Data management

10.3.1 Soundness (Reliability)

- With respect of systematic pooling of and signal detection out of spontaneous reports the successful implementation of the EudraVigilance network is essential.
- To ensure reliable processes the respective SOPs should be applied. Validated IT solutions should be used.
- It is important to have an overview of available sources of information, therefore all necessary data should be accessible under one user interface.

10.3.2 Speed

- Unnecessary duplication of work should be avoided.
- Good IT infrastructure incl. software is necessary to enable agencies to do as many routine tasks as possible electronically.

10.3.3 Workload

- To avoid unnecessary duplication, it should be clarified what work is necessary at the national level, e.g. in the analysis of PSURs.
- Future increases in requirements (e.g. data warehouse) should be kept in mind when calculating the necessary personnel and technical resources.

10.4 Signal detection

10.4.1 Soundness

- It is necessary to adopt procedures for signal detection to the specific situation (in terms of risk, available data etc.). A common understanding of signal detection is needed and should be adhered to in order to improve the agencies trust in results of the others' signal detection and safety issue assessments.
- It should be recognised that spontaneous reports are in no way representative for the population; this means that even one single report might be a signal, and information other than from spontaneous reporting has to be used proactively. The sequential approach should be replaced by a cyclic approach.
- With respect of systematic pooling of and signal detection out of spontaneous reports the successful implementation of the EudraVigilance network is essential.
- Systematic development and exchange of methods to analyse routine and supporting data (ICSRs, PSURs, consumption data, etc., and combinations thereof) is necessary. Data-mining techniques and institutionalized follow-up procedures may help to make better use of available research, hopefully leading to better, and earlier, signal detection.
- Specific emphasis should laid on statistical tools for small numbers of reports.
- It should be ensured that MAHs fulfil their obligation to adequately and timely identify safety signals concerning their signals. Inspections are one way to check for their ability to do so.

10.5 Safety issue assessment

10.5.1 Co-operation

- The work load related to assessment should be distributed more equally with respect to the size of the countries. The roles and responsibilities should be refined to increase the use of existing assessments from other agencies.
- The agencies should be given the resources to carry out assessments for NAPs on their market by themselves, using all available sources of information including EudraVigilance.
- No decision about a signal should rely on only a single person. Assessment reports from other agencies should be used systematically.

10.5.2 Access to external experts

- Access to national external expert(s)/committee, in smaller countries also to international experts, should be guaranteed for routine and in exceptional cases.

10.6 Decision-making

10.6.1 Speed

- The immediate access to decision-makers (within agency or in a higher-level authority) should be guaranteed. A reliable structure should ensure this vertical collaboration and that decision-makers have all necessary info incl. a suggestion for regulatory action.
- The speed of decision-making on the EU-level should be increased. Time-consuming processes within the Commission after having received an opinion should be identified.
- The cooperation of PhVWP and CHMP should be revised: More competences for the PhVWP as the primary expert group for pharmacovigilance should be considered.

10.7 Communication and action to protect public health

10.7.1 Speed of implementation

- Communications should be prepared in time. The respective communication channels have to be kept prepared for potential crises including product withdrawals.
- Already drafts of communications should be prepared and exchanged with other agencies after an opinion has been submitted to the decision-makers. This should include early communication with all necessary target groups. The respective SOPs should be adhered to.
- To build professional communication strategies with targeted information for the different groups of stakeholders, the agencies' press officers should be involved, who should collaborate to make best use of their competences and avoid duplication of work.

10.7.2 Harmonisation of communications

- The regulatory system should guarantee that the outcome of EU assessments is implemented in a harmonized way on the national level.
- The coordination between agencies and MAHs should be improved, especially with regard of the time of publication on safety issues.

10.7.3 Outcomes of regulatory action

- Effective strategies for risk communication towards prescribers should be a topic that should feature on any agenda of risk management strategies.
- It should be strived to influence clinical guidelines and patient information leaflets, not only SPCs.
- Safety information should be included into HCPs' day-to-day information (formulary…).

- The outcomes of regulatory action should be audited.
- When managing drug safety issues, considering the impact of action taken on patients is of key importance. Abrupt discontinuation is often unwanted and requires monitoring of patients after the announcement of the safety alert. Effective regulatory management of post-event (e.g. safety restrictions) drug use is to be warranted.
- Major action should be accompanied by an evaluation of the impact of safety warnings on clinical practice. Careful monitoring of drug utilization will help regulators to better anticipate on developments relevant for drug safety.

10.8 Core recommendations

From the present research, we 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 (ICSRs, PSURs, registries, consumption data, safety studies etc.) and respective resources that are devoted to these tasks 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…).

Annex 1: Literature

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Annex 2: Questionnaire for Agency survey

19.07.2005

"Assessment of the European Community System of Pharmacovigilance"
Agency Survey 2005

Please complete and return this form by July 31, 2005

Your agency:	
Please give details of the person we should contact with any question about this return	
Name of contact person:	
Department:	
Telephon number:	
E-mail address:	

Important:

The survey concerns the Pharmacovigilance unit of the agency including **Human**
OTC, generics, herbal and other drugs, but no non-drug products. If not requested otherwise, please refer only to **resources that you have in your own agency** (and not in Regional Centres for Pharmacovigilance, e.g.), and staff that is paid by your agency.
Please provide the requested information for the **complete year 2004** (01 January to 31 December 2004).
Please enter the requested information only in the white fields of this form.
If adequate, please check boxes by an "x".
If you wish to split the questionnaire into separate chapters please always include the cover sheet.
Please return the completed questionnaire by 31 July 2005 to bernhard.buehrlen@isi.fraunhofer.de.
It is easier for us to get the data electronically, but you can also print the PDF-document and return it by **FAX (+49 721 6809 315).**
Thank you very much for your support!
Some of the questions are market with "**ERMS**" and a number. This means that the figures have been asked for in the ERMS-survey so that the **Agencies in the New Member States** will still have the data for 2004 in their records. Please enter them in our questionnaire too! The **Agencies in the Old Member States** have participated in the ERMS survey already in 2002 and would now be asked for newer (2004) data.

	yes
	x

Further information:

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Abbreviations:

CHMP	Committee for Medicinal Products for Human Use
EMEA	European Medicines Agency
EU	European Union
EEA	European Economic Area (i.e. EU-25 + Iceland, Liechtenstein, Norway)
ERMS WG	Heads of Agencies European Risk Management Strategy Working Group
ICH	International Conference on Harmonisation
ICSR	Individual Case Safety Reports
MAH	Marketing Authorisation Holder
MedDRA	Medical Dictionary for Regulatory Affairs
NUIS	Non Urgent Information System
PhV	Pharmacovigilance
PhVWP	Pharmacovigilance Working Party
PSUR	Periodic Safety Update Report
RAS	Rapid Alert System
SPC	Summary of Product Characteristics
WHO	World Health Organisation

Chapter A: Framework conditions

1) How much time (%) of the PhV unit is spent on pharmacovigilance work where your Agency is:

ERMS 7

a) Acting for the Community (as Rapporteur)		%
b) Acting for the Community (as Reference Member State)		%
c) Acting on a nationally licensed product		%
d) Work that is not product-specific		%
Sum:	**100**	%

2) How many regulatory approvals for NMEs (New Molecular Entities) were granted in your home country?

	2003	2004
a) National approvals in your home country		
b) Mutual recognition procedure		
ba) Thereof: Mutual recognition procedure with your country as Reference Member State		
c) Centralized procedure with your country as rapporteur		

		2004	
3)	**How many physicians work in your home country?**		
	a) in general practice or as specialists outside hospitals?		number
	b) inside hospitals?		number
		2004	
4)	**How many companies hold at least one marketing authorisation in your home country?**		number
		2004	
5)	**How many companies have a production plant in your home country?**		
	a) as parts of an international company with subsidiaries in at least one other country?		number
	b) as domestic company without subsidiaries in other countries?		number
		2004	
6)	**How many products are authorised in your country?**		
	a) Number of nationally authorised products in your country		number
	b) Number of MR authorised products in your country		number
	c) Number of centrally authorised products in your country		number

Chapter B: Ressources for PhV

7)	**What was the annual budget of your Agency in 2004** (total; not including budget for regional centres)**?**		Mio €	
8)	**How many staff are directly employed in your Agency (total)?** *Please give numbers of staff in real Full-time equivalents (FTE), e.g.: 1 Person with a full-time contract working only for the task in question would equal 1 FTE, but if she/he only works with 80% of her/his time fort he tasks in question this would equal 0.8 FTE.*		FTE	
9)	**How many staff in your Agency are directly employed in pharmacovigilance?** (not including regional monitoring centres)			
	a) total		FTE	ERMS 1
	Thereof:			
	b) administrative		FTE	ERMS 3
	c) scientific		FTE	
	Of scientific:			
	ca) Pharmaceutical		FTE	ERMS 3
	cb) Medical		FTE	
	cc) Epidemiology		FTE	
	cd) Other (please specify):		FTE	
	cda)		FTE	
	cdb)		FTE	
	cdc)		FTE	
	cde)		FTE	
10)	**How many staff are directly employed in each process?** (Some may be involved in more than one process, then please count in each of the categories.)			ERMS 2
	a) Data collection and data entry		Persons	
	b) Data management		Persons	
	c) Risk assessment		Persons	
	d) Regulatory action (relating to pharmacovigilance issues)		Persons	
	e) Risk communication		Persons	
	f) Audit and quality assurance		Persons	
	g) Monitoring compliance with industry on reporting requirements		Persons	

11)	**Do you contract out any of your pharmacovigilance assessment work?** (i.e. for PSUR and safety related variations assessment)	yes	no	ERMS 6
	a) ...to external academics			
	b) ...to health professionals in health service			
	c) ...to regulatory consultants			
	d) ...to regional centres for PhV			
	e) ...to others (please specify)			

		yes	no	
12)	**Are regional centres in operation?**			
	a) Number of regional centres		centres	
	b) Please describe their responsibility shortly:			
	Routine work:	yes	no	
	ba) data collection and management			
	bb) signal detection			
	bc) safety issue assessment			
	bd) decision making			
	be) communication			
	bf) inspection of MAHs			
	Specific tasks:	yes	no	
	bg) scientific studies on PhV issues			
	bh) informal advice for the national agency			
	bi) other tasks (please specify):			
	c) Total number of staff (sum of all regional centres) for routine work		persons	
	d) other resources:			
	e) number of ADR reports collected by regional centres in 2004		reports	

13) Describe the external expertise available in your country distinguishing the following areas of expertise:

	available in (national) Agency	in regional centre	external experts	not at all in the country
Experimental toxicology				
Animal studies				
In vitro testing				
(Clinical) pharmacology				
Medicine				
Pharmacoepidemiology/ Drug utilisation				
Epidemiology				
Statistics				
Human ADRs to veterinary medicinal products (only in the case of veterinary medicinal products)				
Design of pharmacovigilance plans				
Regulatory affairs				

		yes	no	
14)	**Do you have an expert committee dedicated to pharmacovigilance?**			ERMS 11
	a) If yes, how many times did it meet in 2004?		times	
		yes	no	
15)	**This committee is not only responsible for PhV, but for marketing authorisation and variations (e.g.) as well (e.g. Marketing Authorisation Board)**			ERMS 11
16)	**What is the IT-system of the postmarketing unit like?**			
	Number of PCs		PCs	
		yes	no	
	Sufficient number of PCs available for all scientific and technical staff			
	Local area network for the PCs available			
	Permanent Internet-access available			
	Sufficient support for maintenance of the IT systems available			

		totally sufficient				very insuffi-cient
17)	**How would you assess your IT-ressources (hardware, software, electronic communication)?**					

Chapter C: Definitions and standards

		yes	no
18)	**Is MedDRA implemented as dictionary for coding of reports in your database?**		

19) Existing guidance documents

	exists in national version		exists from EU	
	yes	no	yes	no
Obligations of MAH				
Obligations of NCA				
Collaboration with other authorities and int. health institutions				
Quality management within the agency				
Qualification of MAH				
Standard Operation Procedure (SOP) for:				
a) Data collection				
b) Data management				
c) Signal detection/ Safety issue assessment				
d) Decision-making				
e) Communication with MAHs				
f) Communication with Health care professionals				
g) Crisis management				
h) Feedback to reporters				
i) Development and maintenance of SOPs				

20) Implementation of new requirements from Oct. 2005 on…

	yes	no	
a) … already in place?			
b) … scheduled to be operable when?			Month/ Year

Chapter D: Processes

Chapter D1: Data collection

21) How do reporters submit reports on ADRs? ERMS 14

a) Paper		% of ICSRs
b) Electronic		% of ICSRs
c) via web-site of the National Agency or of a Regional centre		% of ICSRs
d) Other, e.g. telephone		% of ICSRs

22) How many national ICSRs in total are ERMS 15

a) contained totally in your database of ADRs		reports
aa) thereof received in 2003		reports
ab) thereof received in 2004		reports

23) How many reports of suspected ADRs did you receive in 2004 through your national spontaneous reporting scheme?

a) Total		reports
thereof:		
b) received from MAHs		reports
c) direct from doctors/dentists		reports
d) direct from pharmacists		reports
e) direct from nurses		reports
f) direct from patients		reports
g) direct from coroners		reports
h) direct from health professional body		reports
i) Other (please specify):		
		reports

ERMS 13

24) How many reports of suspected ADRs did you receive in 2004 through your national spontaneous reporting scheme?

a) serious expected		reports
b) serious unexpected		reports
c) nonserious expected		reports
d) nonserious unexpected		reports

25) How many ICSRs did you receive in 2004 …

a) on nationally authorised medicines		reports
b) from your country as concerned MS		reports
c) from your country as reference MS		reports

26)	**How many national ICSRs did you receive in 2004 on children?**		reports				
27)	**How many PSURs did you receive in 2004 …**						ERMS 20
	a) National PSURs		Number				
	b) Mutual recognition when your counttry is reference MS		Number				
	c) Centralised when your country is rapporteur		Number				
28)	**How many PSURs have you assessed in 2004?**		Number				
29)	**What is the number of ICSRs from your country with incomplete data (i.e. less than 4 minimal data points)?**		Number				
		very good					very bad
30)	**How well has your routine data-collection prepared you for the last pharmacovigilance crisis?**						
		very useful					only margina l-ly useful
31)	**How useful are routine data from your country (ICSRs and PSURs together) for safety issue assessment compared to other information?**						

Chapter D2: Data management

		yes	no		
32)	**Do you use an electronic database to manage national ICSRs?**				
33)	**Which database software do you use to manage national ICSRs?**				
		yes	no		
34)	**Is EudraVigilance already implemented?**				
	a) If not, when will it be fully operable from your Agency's side?			Month/ Year	
		yes	no		
35)	**Have you implemented the standards required for the electronic transmission of ICSRs?**				ERMS 4
		yes	no		
36)	**Is electronic reporting by MAH due October 2005 in place?**				
	if not: When will it be operable?			Month/ Year	
37)	**What is the share of reports from MAHs transmitted electronically of total reports from MAH (average of 1st half of 2005)**		%		
		yes	no		
38)	**Is reporting of suspected ADRs by healthcare professionals mandatory?**				ERMS 13C
	a) If so, do you apply the law to all Health care professionals?				
	b) Please specify (mandatory for…; exceptions….; enforcement or not etc.)				
39)	**How long does is take to assess PSURS (days from reception to finished assessment) on average?**		days		
		adequat e			far too slow
40)	**How do you assess the time between data entry and transmission to EMEA or MAHs?**				

Chapter D3: Signal detection

41) Are there other data that you are using or could use for signal detection or safety issue assessment in your country?
(sources do not have to cover the whole population)

similar ERMS 18-19

	Exist in country		Agency has access to			Used		
a) Population-based health/disease registries (=exposure-outcome databases):	yes	no	yes, always	yes, but only in exceptional cases	no, never	routinely	in exceptional cases	never
aa) Inpatient medical care								
ab) Outpatient medical care								
ac) Cancer								
ad) Causes of death								
ae) Intra uterine drug exposure								
af) Malformations in newborns								

	Exist in country		Agency has access to			Used		
b) Data on consumption of medicines?	yes	no	yes, always	yes, but only in exceptional cases	no, never	routinely	in exceptional cases	never
a) Sales data								
b) Prescription data								
ba) - non-hospital								
bb) - hospital								
bc) only for reimbursed medicines								
bd) prescription data by age								
be) ...by sex								
bf) ...by geographic region								

	Exist in country		Agency has access to			Used		
c) Other population-based data sources (please specify):	yes	no	yes, always	yes, but only in exceptional cases	no, never	routinely	in exceptional cases	never

42) Do you have plans to obtain some of the data sources at which you do not have access at the moment?

yes	no

43) Do you have the capability to link prescription registries with other registries which include health outcomes? ERMS 19C

yes	no

44) Do you have experience in conducting pharmacoepidemiological studies using such data? ERMS 18B

yes	no

45) Do you evaluate reporting rates (calculated from spontaneous ADRs and usage data)? ERMS 19A

yes	no

46) How many pharmacoepidemiology studies, post-authorisation surveillance studies or phase IV trials have been carried out last year with a sample from your country, taken all sponsors together (public and private)?

	2004	
a) total number in 2004		Number
b) thereof initiated by the Agency		Number

47) Has your Agency initiated or carried out ad hoc pharmacoepidemiology studies in 2004 when a signal needed confirmation or quantification? ERMS 23

	yes	no
a) Using in-house expertise		
b) Via collaboration with an academic department		
c) Via the marketing authorisation holder		

		yes	no	
48)	**Has your Agency initiated or carried out pharmacoepidemiological studies for early post-marketing surveillance of new products in 2004?**			ERMS 24
	a) Using in-house expertise			
	b) Via collaboration with an academic department			
	c) Via the marketing authorisation holder			
49)	**Are clinical trial adverse event (AE) reports collected by the authority and available to those staff responsible for pharmacovigilance of marketed products?**			
50)	**Is information collected on ADRs with compassionate use / named patient use of products?**			

51) What published medical and scientific literature (including databases of literature) are searched / screened and how often?

Journal/Database/Source	screened x times per year

		yes	no
52)	**Are data / information on post-authorisation safety studies routinely collected and recorded?**		
53)	**Are data/information on phase IV efficacy trials routinely collected and recorded?**		
54)	**Are data/information on preclinical studies routinely collected and recorded?**		
55)	**For information from other regulatory authorities, are data / information routinely collected and recorded?**		
56)	**Do you have all of the following data directly accessible under one user interface: national ICSRs, national PSURs, reports from literature, prescription or consumption data, and premarketing safety data?**		

		always adequate				often very inadequate
57)	**How do you assess the statistical tools that you have available for signal detection?**					

		yes	no
58)	**Do you have adequate statistical tools for small numbers of cases that you can run on your national data?**		

Chapter D4: Safety issue assessment

		yes	no
59)	**Are external experts (besides the Pharmacovigilance Working Party) routinely involved in the assessment of safety issues?**		

		very easy				(nearly) impos-sible
60)	**How easy is it for you to receive support from external experts in routine work?**					

		always when necessary				(nearly) impos-sible
61)	**How easy is it for you to receive support from external experts in exceptional cases?**					

		yes	no
62)	**Do you have the capabilities in your country to identify and assess signals without help from other agencies?**		

		very little				very much
63)	**How much work is done in signal detection and safety issue assessment within your country and at the same time in other MS or on EU level?**					

		2004	
64)	**How many assessment reports were written by your Agency in 2004?**		Number

		very good				very bad
65)	**How do the MAHs in your country comply with their obligation to analyse safety signals?**					

Chapter D5: Decision-making

		always				seldom
66)	**Adequate decisions are found for safety issues…**					
	a) for Nationally authorised drugs					
	a) for Mutual Recognition authorised drugs					
	a) for Centrally authorised drugs					

		always				seldom
67)	**Decisions are found for safety issues in adequate time…**					
	a) for Nationally authorised drugs					
	a) for Mutual Recognition authorised drugs					
	a) for Centrally authorised drugs					

		very good				very bad
68)	**How transparent to your Agency is the process of decision-making on safety issues in the companies located in your country?**					

Chapter D6: Communication/Action

		yes	no
69)	**Do you *routinely* inform the following stakeholder groups on general issues of drug safety?**		
	a) Individual doctors or doctors in hospitals		
	b) Medical associations		
	c) Professional journals		
	d) Pharmacists or pharmacists' associations		
	e) Other HCPs		
	f) Patient organisations		
	g) MAHs		
	i) The public/media		
	j) Other groups		

		yes	no
70)	**Whom do you inform *on specific safety issues*?**		
	a) Individual doctors or doctors in hospitals		
	b) Medical associations		
	c) Professional journals		
	d) Pharmacists or pharmacists' associations		
	e) Other HCPs		
	f) Patient organisations		
	g) MAHs		
	i) The public/media		
	j) Other groups		

		yes	no
71)	**Do you always have the best measures to minimize risks from ADRs?**		

		2004	
72)	**How many responses were given to enquiries by HCPs?**		Number
73)	**On how occasions were Dear-doctor-letters sent to HCPs in your country?**		Number
74)	**How many letters were sent to MAHs to amend SPCs?**		Number
75)	**How many variations of SPCs were evaluated?**		Number
76)	**How many inspections of MAHs were carried out where PhV was an issue (at least partially; including inspections that were carried out by other authorities in the coutry)?**		Number
77)	**How many drugs were withdrawn from your national market?**		Number
78)	**How many marketing authorisations were suspended for drugs on your national market?**		Number

		yes	no
79)	**The organisation has the capability of leading EU wide co-ordination of regulatory action and communication of drug safety issues.**		

		adequate				far too slow
80)	**How do you assess the time between the detection of a signal (first discussion within the agency) and reporting (publishing) of decision with respect to this safety issue?**					

		very good				very bad
81)	**How consistent is the communication on safety issues across agencies?**					
82)	**How consistent is the communication on safety issues between agencies on the one side and MAHs and HCPs on the other side?**					

Chapter E: Outcomes

		yes	no
83)	**Do you routinely follow-up the impact of communications?**		

		very good				very weak
84)	**How strong is the influence of the Agency's communications on the doctors' prescription behaviour?**					

85) What are the outcomes of safety-relevant studies using samples from your country (if known)?
Please indicate relevant studies (also from the literature) that were carried out in your country in the last 3 years.

a) Outcome: Incidence of ADR-relevant diseases

	Reference	carried out in year	Outcome (Rates)	Unit: (e.g. per million inhabitants)
aa) Study 1				
ab) Study 2				
ac) Study 3				
ad) Study 4				
ae) Study 5				
af) Study 6				

		please mark
ag)	**There were no such studies in our country in the last 3 years**	

b) Outcome: Mortality due to ADRs

	Reference	carried out in year	Outcome (Rates)	Unit: (e.g. per million inhabitants)
ba) Study 1				
bb) Study 2				
bc) Study 3				
bd) Study 4				
be) Study 5				
bf) Study 6				

		please mark
bg)	**There were no such studies in our country in the last 3 years**	

c) Outcome: Hospitalisations due to ADRs

	Reference	carried out in year	Outcome (Rates)	Unit: (e.g. per million inhabitants)
ca) Study 1				
cb) Study 2				
cc) Study 3				
cd) Study 4				
ce) Study 5				
cf) Study 6				

		please mark
cg)	**There were no such studies in our country in the last 3 years**	

d) Outcome: Quality-adjusted life years (QUALYs) lost due to ADRs?

	Reference	carried out in year	Outcome (Rates)	Unit: QUALYs (e.g. per patient)
da) Study 1				
db) Study 2				
dc) Study 3				
dd) Study 4				
de) Study 5				
df) Study 6				

		please mark
dg)	There were no such studies in our country in the last 3 years	

Chapter F: General aspects

		2004	
86)	What percentage of the staff in the PhV unit has received a training in the last year?		%
87)	How many training measures (internal or external) took place with at least one participant from the agency?		Number

		2004	
88)	How many events have taken place in the last year with participation or support from the Agency to educate reporters/HCPs in pharmacovigilance?		Number
89)	How many bulletins from your agency including safety issues were issued?		Number

		2004	
90)	How many answers to the CHMP were prepared by your Agency?		Number
91)	How many legal documents and guidelines were prepared by your Agency?		Number
92)	How many scientific publications with at least one author from the agency were published in the last year?		Number

		very good				very bad
93)	How does the Agency meet its internal targets for timing and other requirements?					
94)	How do you assess the internal cooperation within the agency (within PhV unit, with pre-marketing departmernt, incl. IT staff)?					
95)	How do you assess the cooperation of your agency with HCPs?					
96)	How do you assess the cooperation of your agency with the MAHs in your country?					
97)	How do you assess the cooperation between the national agencies and the EMEA?					
98)	How strong is the political support for pharmacovigilance in your country in general?	very good				very weak
99)	How do you assess the overall compliance of the the MAHs in your country with the legal requirements?					

Annex 3: Results of Delphi survey on critical success factors

"Assessment of the European Community System of Pharmacovigilance"

19.07.2005

**Analysis: Delphi sheet for critical success factors Round-1:
Values relative to number of respective answers**

**Relevance: How important is the factor for the performance
of the European System for Pharmacovigilance (or parts of it)?**

	Evaluation Round 1: Relevance for...[23]																			
	… quality of the work[24]					… compliance with requirements					… speed ("kinetics")					… work load/costs				
Success factor	**++**	**+**	**0**	**-**	**--**	**++**	**+**	**0**	**-**	**--**	**++**	**+**	**0**	**-**	**--**	**++**	**+**	**0**	**-**	**--**
1. … for Data collection																				
1.1 Comprehensiveness of the data	26%	46%	15%	0%	0%	16%	33%	39%	0%	4%	15%	23%	42%	8%	8%	8%	31%	23%	31%	4%
Mandatory reporting by HCPs	25%	33%	17%	8%	17%	23%	38%	31%	0%	8%	8%	23%	**54%**	8%	8%	8%	31%	23%	31%	8%
Spontaneous reports from pharmacists	27%	**64%**	9%	0%	0%	17%	42%	42%	0%	0%	0%	33%	**67%**	0%	0%	0%	36%	**55%**	9%	0%
Access to FDA data for national agencies	17%	42%	33%	8%	0%	15%	15%	**62%**	0%	8%	15%	15%	**54%**	8%	8%	8%	38%	38%	8%	8%
Access to drug utilisation statistics	**79%**	21%	0%	0%	0%	31%	46%	23%	0%	0%	23%	38%	31%	0%	8%	8%	31%	46%	15%	0%
Access to database of patients' medical records	38%	**62%**	0%	0%	0%	15%	23%	**62%**	0%	0%	15%	38%	31%	8%	8%	31%	23%	15%	31%	0%
Highest-possible number of spontaneous reports	27%	36%	18%	18%	0%	27%	27%	36%	0%	9%	18%	9%	45%	9%	18%	36%	27%	18%	9%	9%
More information from pre-marketing evaluation	23%	**62%**	15%	0%	0%	0%	**58%**	33%	0%	8%	15%	23%	38%	23%	0%	8%	31%	23%	38%	0%
More post-authorisation surveillance studies	**82%**	18%	0%	0%	0%	23%	**62%**	15%	0%	0%	15%	31%	31%	23%	0%	17%	25%	8%	42%	8%

[23] Numbers represent the share of answers in this field of all answers given to this item in the respective dimension.

[24] ++: strong positive influence; 0: not relevant; --: strong negative influence

Patient reporting	8%	**54%**	15%	23%	0%	0%	23%	**69%**	0%	8%	0%	23%	38%	31%	8%	8%	23%	23%	38%	8%
More direct input from patients or patients' organisations	17%	**50%**	33%	0%	0%	0%	23%	**77%**	0%	0%	8%	0%	46%	38%	8%	0%	31%	31%	38%	0%
1.2 Organisation of data collection	35%	36%	15%	8%	0%	15%	36%	38%	0%	0%	8%	31%	44%	8%	0%	12%	19%	35%	23%	4%
Adaptive/stepwise approach tailored to specific safety issue	**58%**	33%	8%	0%	0%	17%	**50%**	33%	0%	0%	8%	42%	42%	8%	0%	8%	42%	25%	25%	0%
Concentrate on best-quality data	**54%**	23%	15%	8%	0%	15%	31%	38%	15%	0%	8%	38%	46%	8%	0%	8%	38%	46%	8%	0%
Pro-active data collection	31%	**69%**	0%	0%	0%	8%	**77%**	15%	0%	0%	31%	23%	38%	8%	0%	15%	23%	8%	46%	8%
Have national database for ICSRs in addition to EudraVigilance	31%	31%	15%	23%	0%	38%	23%	38%	0%	0%	15%	31%	38%	15%	0%	23%	8%	38%	23%	8%
Support in data collection by regional centres for PhV	23%	38%	31%	8%	0%	15%	15%	**54%**	15%	0%	8%	15%	46%	31%	0%	23%	15%	31%	23%	8%
Offer single contact point for MAH in agency for pre- and postmarketing	38%	31%	23%	8%	0%	0%	46%	**54%**	0%	0%	23%	31%	46%	0%	0%	8%	31%	**54%**	8%	0%
Trust in HCPs as data source	8%	**58%**	17%	17%	0%	0%	42%	42%	17%	0%	0%	17%	**75%**	8%	0%	0%	8%	**92%**	0%	0%
Education of reporters	**54%**	46%	0%	0%	0%	46%	23%	31%	0%	0%	8%	46%	38%	8%	0%	15%	15%	31%	31%	8%
2. … for Data management																				
2.1 Electronic processing of data	**54%**	31%	8%	0%	0%	**54%**	38%	15%	0%	0%	**69%**	23%	8%	0%	0%	46%	38%	8%	8%	0%
Sufficient IT-ressources (investments)	**62%**	31%	8%	0%	0%	**54%**	46%	0%	0%	0%	**69%**	23%	8%	0%	0%	46%	46%	8%	0%	0%
Sufficient support for maintenance of IT systems	**54%**	38%	8%	0%	0%	**54%**	23%	23%	0%	0%	**54%**	38%	8%	0%	0%	**54%**	31%	8%	8%	0%
Have all information available electronically	**54%**	23%	23%	0%	0%	46%	38%	15%	0%	0%	**69%**	15%	8%	0%	8%	46%	38%	8%	8%	0%
2.2 Processing of data	25%	42%	8%	0%	0%	15%	38%	38%	0%	0%	17%	**58%**	17%	0%	0%	17%	**54%**	31%	8%	0%
Internal cooperation within the agency	**50%**	42%	8%	0%	0%	8%	**67%**	25%	0%	0%	17%	**83%**	0%	0%	0%	18%	**55%**	27%	0%	0%
Structure of the agency	23%	**62%**	15%	0%	0%	15%	23%	**62%**	0%	0%	15%	**54%**	31%	0%	0%	8%	**54%**	31%	8%	0%
Prioritization (among PSURs…)	25%	**75%**	0%	0%	0%	8%	25%	**58%**	8%	0%	17%	**58%**	25%	0%	0%	8%	**58%**	25%	8%	0%
Amount and quality of data in national database	**58%**	42%	0%	0%	0%	33%	42%	25%	0%	0%	25%	**58%**	17%	0%	0%	17%	33%	42%	0%	8%

Processing of data as fast as possible	17%	25%	42%	8%	8%	23%	38%	38%	0%	0%	31%	**62%**	0%	8%	0%	25%	17%	42%	17%	0%
3. … for Signal detection																				
3.1 Availability of necessary information	31%	**62%**	8%	0%	0%	23%	38%	38%	0%	0%	31%	**62%**	8%	0%	0%	15%	**54%**	23%	0%	8%
Have all data directly accessible under one user interface	31%	**62%**	8%	0%	0%	23%	38%	38%	0%	0%	31%	**62%**	8%	0%	0%	15%	**54%**	23%	0%	8%
3.2 Data analysis	**54%**	46%	0%	0%	0%	25%	25%	**50%**	0%	0%	38%	**50%**	8%	4%	0%	41%	36%	18%	5%	0%
New statistical methods to analyse ICSRs	**58%**	42%	0%	0%	0%	25%	25%	**50%**	0%	0%	42%	42%	8%	8%	0%	45%	36%	18%	0%	0%
Adequate statistical tools also for small numbers of cases	**50%**	**50%**	0%	0%	0%	25%	25%	**50%**	0%	0%	33%	**58%**	8%	0%	0%	36%	36%	18%	9%	0%
3.3 International share of work	**60%**	40%	0%	0%	0%	40%	20%	40%	0%	0%	**60%**	40%	0%	0%	0%	33%	**50%**	0%	0%	17%
4. … for Safety issue assessment																				
4.1 Share of responsibilities	38%	42%	12%	4%	0%	19%	42%	38%	0%	0%	19%	42%	27%	12%	0%	15%	**54%**	0%	23%	8%
Have national capabilities to identify and assess signals without help from other agencies	38%	31%	23%	8%	0%	23%	38%	38%	0%	0%	23%	38%	31%	8%	0%	31%	23%	15%	23%	8%
International cooperation/share of work	**77%**	8%	15%	0%	0%	31%	8%	**62%**	0%	0%	38%	46%	15%	0%	0%	31%	46%	0%	15%	8%
Supplement MAHs' primary obligation to analyse signals	31%	**54%**	8%	8%	0%	15%	46%	38%	0%	0%	15%	46%	23%	15%	0%	0%	**62%**	0%	31%	8%
Independence of the assessment from the MAH	38%	**54%**	8%	0%	0%	8%	**69%**	23%	0%	0%	0%	31%	**54%**	15%	0%	0%	**62%**	0%	23%	15%
4.2 Expertise	**58%**	33%	8%	0%	0%	25%	31%	**50%**	0%	0%	25%	42%	25%	8%	0%	25%	8%	**50%**	17%	0%
Have expertise for assessment of signals in-house	**62%**	31%	8%	0%	0%	31%	**54%**	15%	0%	0%	46%	46%	8%	0%	0%	25%	33%	25%	17%	0%
External review of assessments	23%	46%	31%	0%	0%	0%	31%	**62%**	8%	0%	8%	15%	46%	31%	0%	8%	8%	**54%**	31%	0%
Availability of external experts within the country	**58%**	33%	8%	0%	0%	25%	25%	**50%**	0%	0%	25%	42%	25%	8%	0%	25%	8%	**50%**	17%	0%
4.3 Structures	0%	9%	**64%**	18%	9%	0%	9%	**55%**	27%	9%	0%	0%	**55%**	36%	9%	10%	20%	40%	20%	10%
Different requirements for NAPs, MRPs, CAPs	0%	9%	**64%**	18%	9%	0%	9%	**55%**	27%	9%	0%	0%	**55%**	36%	9%	10%	20%	40%	20%	10%

5. … for Decision-making																				
5.1 Decision-making in legal bodies	23%	18%	25%	8%	0%	15%	18%	42%	8%	0%	8%	18%	**64%**	17%	0%	0%	25%	**55%**	9%	9%
Do only make decisions if the responsible MAH does not	9%	9%	27%	9%	45%	0%	18%	27%	18%	36%	0%	9%	**73%**	9%	9%	9%	18%	**55%**	9%	9%
Decision-making as joint effort between MAH and agency	23%	38%	23%	8%	8%	15%	23%	46%	8%	8%	8%	38%	38%	15%	0%	0%	42%	**50%**	8%	0%
Take into account costs of decisions/actions (e.g. on 3rd countries)	18%	18%	**64%**	0%	0%	0%	9%	**91%**	0%	0%	0%	0%	**64%**	27%	9%	0%	9%	45%	36%	9%
Lean decision-making with only few steps or involved committees	**50%**	17%	25%	8%	0%	33%	17%	42%	8%	0%	**67%**	25%	0%	8%	0%	9%	27%	45%	9%	9%
Less influence of pre-marketing units in decision-making	0%	0%	36%	**64%**	0%	0%	0%	**55%**	45%	0%	0%	18%	**64%**	18%	0%	0%	33%	**67%**	0%	0%
Find actions specific for safety issue	**55%**	36%	9%	0%	0%	36%	45%	18%	0%	0%	27%	18%	27%	27%	0%	18%	0%	**64%**	0%	18%
Follow-up impact of decisions	**50%**	**50%**	0%	0%	0%	17%	**58%**	25%	0%	0%	8%	0%	**75%**	17%	0%	0%	25%	**58%**	17%	0%
5.1 Decision-making in companies	17%	**58%**	25%	0%	0%	17%	42%	42%	0%	0%	0%	17%	**83%**	0%	0%	0%	17%	**75%**	0%	8%
Transparent decision-making within MAH	17%	**58%**	25%	0%	0%	17%	42%	42%	0%	0%	0%	17%	**83%**	0%	0%	0%	17%	**75%**	0%	8%
6. … for Communication/Action																				
6.1 Early communication	39%	36%	4%	13%	8%	16%	36%	32%	8%	8%	20%	28%	**52%**	0%	0%	0%	20%	40%	36%	4%
Communicate already before decision is taken	8%	42%	8%	25%	17%	8%	25%	33%	17%	17%	17%	25%	**58%**	0%	0%	0%	17%	42%	33%	8%
Communicate not only reactively	**69%**	31%	0%	0%	0%	23%	46%	31%	0%	0%	23%	31%	46%	0%	0%	0%	23%	38%	38%	0%
6.2 Communication to all stakeholders	**54%**	44%	0%	0%	0%	48%	31%	23%	0%	0%	8%	19%	46%	27%	0%	0%	23%	38%	27%	8%
Communicate to patients (patients' organisations) directly	38%	**54%**	8%	0%	0%	15%	38%	46%	0%	0%	15%	23%	31%	31%	0%	0%	31%	15%	46%	8%
Contact professional journals before they publish on safety issues	23%	46%	31%	0%	0%	0%	23%	**77%**	0%	0%	8%	15%	46%	31%	0%	0%	23%	23%	46%	8%
Consistency of communications across stakeholders and countries	**75%**	25%	0%	0%	0%	**54%**	31%	15%	0%	0%	8%	31%	46%	8%	8%	0%	23%	46%	23%	8%
Stronger harmonisation of implementation of decisions	**50%**	**50%**	0%	0%	0%	46%	31%	23%	0%	0%	0%	15%	46%	38%	0%	0%	31%	31%	31%	8%

Communicate on risk-benefit-ratios, not only on risk	**77%**	23%	0%	0%	0%	**54%**	23%	23%	0%	0%	0%	8%	**62%**	23%	8%	0%	15%	**69%**	8%	8%
Specific crisis communication	**58%**	42%	0%	0%	0%	**50%**	33%	17%	0%	0%	17%	**58%**	17%	8%	0%	0%	8%	**75%**	17%	0%
6.3 Impact of communications/actions	**50%**	44%	8%	0%	0%	38%	35%	38%	0%	0%	8%	23%	**54%**	8%	8%	4%	35%	35%	23%	12%
Stronger influence on HCPs' behaviour	23%	**69%**	8%	0%	0%	15%	46%	38%	0%	0%	8%	23%	**62%**	8%	0%	0%	31%	38%	15%	15%
Influence clinical guidelines and PILs, not only SPCs	15%	**69%**	8%	8%	0%	15%	46%	38%	0%	0%	0%	23%	**54%**	15%	8%	0%	23%	38%	23%	15%
Supervise/control communication of MAHs	15%	**54%**	31%	0%	0%	15%	38%	46%	0%	0%	0%	15%	**54%**	23%	8%	8%	8%	46%	23%	15%
Stronger control of MAHs' compliance	46%	31%	23%	0%	0%	46%	23%	31%	0%	0%	8%	0%	**69%**	8%	15%	8%	15%	31%	23%	23%
Have the right tools to minimize risk	**58%**	42%	0%	0%	0%	42%	42%	17%	0%	0%	17%	**58%**	17%	8%	0%	8%	42%	25%	25%	0%
Guidance for good communication practice	**54%**	38%	8%	0%	0%	38%	31%	31%	0%	0%	8%	**62%**	23%	0%	8%	8%	46%	31%	15%	0%
Advice from communications experts	**54%**	46%	0%	0%	0%	38%	8%	**54%**	0%	0%	17%	33%	42%	8%	0%	0%	42%	**50%**	0%	8%
Follow-up of the impact of communications/actions	**62%**	38%	0%	0%	0%	38%	23%	38%	0%	0%	8%	0%	**77%**	8%	8%	0%	38%	23%	31%	8%
7. … for performance in general																				
7.1 Legal framework	42%	36%	23%	0%	0%	25%	46%	30%	0%	0%	0%	25%	**54%**	8%	0%	8%	23%	**54%**	8%	0%
Contents of legislation and guidelines	45%	36%	18%	0%	0%	40%	**50%**	10%	0%	0%	0%	40%	**60%**	0%	0%	10%	40%	40%	10%	0%
Optimise conflicting legal framework	**62%**	38%	0%	0%	0%	45%	**55%**	0%	0%	0%	18%	36%	36%	9%	0%	18%	18%	**64%**	0%	0%
European legislation becomes nationally binding law incl. penalties for non-compliance	36%	27%	27%	9%	0%	30%	30%	30%	10%	0%	0%	40%	**50%**	10%	0%	0%	20%	**50%**	30%	0%
Take into account specific national requirements	0%	**54%**	23%	8%	15%	0%	46%	38%	8%	8%	0%	0%	**54%**	38%	8%	0%	23%	**54%**	8%	15%
Control over industry, power to enforce requirements	46%	31%	23%	0%	0%	23%	**54%**	23%	0%	0%	0%	23%	**69%**	0%	8%	8%	23%	**69%**	0%	0%
Stronger political support for PhV	42%	**50%**	8%	0%	0%	25%	33%	42%	0%	0%	17%	8%	**67%**	8%	0%	8%	17%	**58%**	17%	0%

Solve problems with different national languages	25%	33%	42%	0%	0%	17%	33%	**50%**	0%	0%	25%	25%	42%	8%	0%	33%	25%	25%	8%	8%
7.2 Staff	**69%**	31%	0%	0%	0%	42%	38%	15%	0%	0%	8%	**54%**	23%	0%	0%	15%	**50%**	23%	8%	0%
Number of internal staff in agency	46%	46%	8%	0%	0%	31%	**54%**	15%	0%	0%	23%	**54%**	23%	0%	0%	42%	**50%**	0%	8%	0%
Continuous education of staff	**77%**	23%	0%	0%	0%	**54%**	38%	8%	0%	0%	8%	**69%**	15%	8%	0%	15%	**54%**	23%	8%	0%
Include PhV into university education	**69%**	31%	0%	0%	0%	42%	8%	**50%**	0%	0%	8%	25%	**67%**	0%	0%	0%	25%	**58%**	17%	0%
7.3 General quality	46%	46%	8%	0%	0%	38%	33%	33%	0%	0%	0%	46%	46%	8%	0%	0%	38%	23%	8%	0%
Internal quality management programme of the agency	**54%**	46%	0%	0%	0%	**54%**	38%	8%	0%	0%	0%	46%	46%	8%	0%	0%	**54%**	15%	31%	0%
Avoid duplication of work	46%	38%	15%	0%	0%	38%	23%	38%	0%	0%	38%	46%	15%	0%	0%	23%	38%	23%	8%	8%
Public trust in the system	42%	**50%**	8%	0%	0%	33%	33%	33%	0%	0%	0%	0%	**92%**	8%	0%	0%	17%	**75%**	8%	0%
Please give and evaluate additional important indicators:																				
Advisor2																				
public understanding of risk	100%	0%	0%	0%	0%	0%	100%	0%	0%	0%	100%	0%	0%	0%	0%	0%	0%	0%	100%	0%
expertise for design of pharmacovigilance plans	100%	0%	0%	0%	0%	100%	0%	0%	0%	0%	100%	0%	0%	0%	0%	100%	0%	0%	0%	0%
routine outcome measures	100%	0%	0%	0%	0%	100%	0%	0%	0%	0%	0%	0%	100%	0%	0%	0%	0%	100%	0%	0%
Advisor5																				
Jobs at the nationl agency attractive for "the best people"	100%	0%	0%	0%	0%	0%	0%	100%	0%	0%	0%	100%	0%	0%	0%	0%	100%	0%	0%	0%

Annex 4: Results of Delphi survey on performance indicators

"Assessment of the European Community System of Pharmacovigilance"	
19.07.2005	
	Analysis: Delphi sheet for performance indicators Round-1: Values relative to number of respective answers
Relevance:	**How important is the indicator to obtain a valid picture of the performance of the European System for Pharmacovigilance?**
	3: very relevant … 0: not relevant
Practicability:	**How easy is it to obtain the data for this indicator?**
	3: very easy to measure … 0: measurable only at very high costs We suppose that the data would have to be collected by the national agency or come from other sources. Please assume the availability of data in the country/region for which your agency is r
Interpretation:	**How easy is it to interpret the results?**
	3: very easy to interpret … 0: nearly not interpretable

	Evaluation Round 1[25]											
	Relevance				**Practicability**				**Interpretation**			
Performance indicator	**3**	**2**	**1**	**0**	**3**	**2**	**1**	**0**	**3**	**2**	**1**	**0**
1. ...for the input												
1.1 Comprehensiveness of the data												
Total number of ICSRs from your country received in last year	**67%**	22%	11%	0%	**88%**	0%	13%	0%	**56%**	22%	22%	0%
Number of ICSRs from your country received in last year from MAHs	**56%**	33%	0%	11%	**75%**	25%	0%	0%	**67%**	22%	0%	11%
Number of ICSRs from your country received in last year direct from HCPs	**75%**	25%	0%	0%	**71%**	14%	14%	0%	**67%**	11%	22%	0%
Number of ICSRs from your country received in last year direct from patients	13%	25%	25%	38%	**50%**	0%	33%	17%	25%	0%	38%	38%
Number of ICSRs from your country received in last year direct from pharmacists	**50%**	33%	0%	17%	**100%**	0%	0%	0%	**67%**	17%	0%	17%
Number of ICSRs from your country received in last year direct from other HCPs	33%	**50%**	0%	17%	**100%**	0%	0%	0%	**67%**	17%	0%	17%
Number of cases received/total number of ICSRs from your country	**50%**	38%	0%	13%	**71%**	0%	14%	14%	**63%**	13%	13%	13%

[25] Numbers represent the share of answers in this field of all answers given to this item in the respective dimension.

% of serious ICSRs from your country	**78%**	11%	11%	0%	**75%**	13%	13%	0%	**63%**	38%	0%	0%
% of ICSRs from your country as concerned MS	**50%**	25%	13%	13%	29%	29%	29%	14%	25%	**50%**	13%	13%
% of ICSRs from your country as reference MS	**50%**	25%	13%	13%	29%	29%	29%	14%	25%	**50%**	13%	13%
Number of PSURs received by origin and type of product	44%	0%	**56%**	0%	**63%**	25%	13%	0%	33%	11%	**56%**	0%
Number of studies carried out on national database/ target number for database studies	38%	38%	25%	0%	25%	25%	38%	13%	**50%**	25%	13%	13%
1.2 Quality of the data												
% of PSURs that comply with E2C	22%	**56%**	22%	0%	0%	29%	**57%**	14%	0%	**63%**	38%	0%
Number of ICSRs from your country with incomplete data (i.e. less than 4 minimal data points)	38%	38%	25%	0%	29%	43%	29%	0%	25%	38%	25%	13%
Number of interventions of medical assessor because of incomplete ICSRs from your country	25%	**50%**	25%	0%	14%	43%	43%	0%	29%	29%	43%	0%
Score for the quality of the spontaneous ICSRs from your country from MAHs/HCPs/others	38%	38%	25%	0%	0%	29%	**57%**	14%	0%	25%	**75%**	0%
1.3 Ressources												
Number of staff in full-time-equivalents	**63%**	38%	0%	0%	**56%**	33%	11%	0%	38%	25%	38%	0%
Number of scientists in full-time-equivalents	**56%**	33%	11%	0%	40%	**50%**	10%	0%	25%	38%	25%	13%
Number of staff per population	29%	29%	29%	14%	43%	43%	0%	14%	14%	43%	29%	14%
Annual budget of the agency	13%	**75%**	13%	0%	**56%**	22%	11%	11%	38%	13%	**50%**	0%
Number of Regional centres in your country	13%	**50%**	25%	13%	**50%**	25%	25%	0%	13%	38%	38%	13%
Total number of staff (sum of all regional centres) for routine work	33%	44%	22%	0%	**56%**	33%	11%	0%	25%	**50%**	25%	0%
Rating-scale: Difficulties in hiring new scientific staff (very easy...very difficult)	33%	44%	22%	0%	33%	22%	44%	0%	25%	13%	**63%**	0%
1.4 Framework conditions												
Number of nationally authorised products in your country	33%	11%	44%	11%	**70%**	20%	10%	0%	40%	10%	**50%**	0%
Number of MR authorised products in your country	22%	44%	22%	11%	**70%**	20%	10%	0%	40%	20%	40%	0%
Number of centrally authorised products in your country	33%	33%	22%	11%	**89%**	11%	0%	0%	40%	20%	40%	0%
Number of physicians in your country	0%	22%	22%	**56%**	**60%**	30%	10%	0%	22%	22%	33%	22%
Pharmaceutical consumption by drug classes	**60%**	0%	30%	10%	**60%**	40%	0%	0%	33%	33%	33%	0%
Pharmaceutical sales by drug classes	40%	30%	20%	10%	**50%**	20%	30%	0%	33%	11%	**56%**	0%

2. ...for the processes												
2.1 Data collection												
Rating-scale: Usefulness of routine data from your country for safety issue assessment compared to other information (very useful…only marginally useful)	**50%**	38%	13%	0%	38%	13%	**50%**	0%	38%	25%	38%	0%
Rating-scale: Access to all necessary data (very easy…very difficult)	25%	**63%**	13%	0%	13%	13%	**63%**	13%	13%	13%	**75%**	0%
2.2 Data management												
Number of ICSRs processed	**56%**	44%	0%	0%	44%	44%	11%	0%	22%	**56%**	22%	0%
Time to assess PSURS (days from reception to finished assessment)	**67%**	11%	22%	0%	25%	38%	38%	0%	22%	33%	44%	0%
Rating-scale: IT-ressources: hardware, software, electronic communication (totally sufficient…very insufficient)	**78%**	22%	0%	0%	22%	33%	44%	0%	11%	44%	44%	0%
Rating-scale: Internal cooperation within agency incl. IT staff (very good…very bad)	**56%**	44%	0%	0%	0%	**56%**	44%	0%	0%	**56%**	44%	0%
Rating-scale: Time between data entry and transmission to EMEA or MAH (adequate … far too slow)	38%	**50%**	13%	0%	**63%**	38%	0%	0%	**50%**	**50%**	0%	0%
2.3 Signal detection												
Rating-scale: Information for signal detection (always sufficient…often very incomplete)	**89%**	11%	0%	0%	0%	**67%**	33%	0%	11%	33%	**56%**	0%
Data sources routinely used for signal detection (routine data, literature, registries…)	**56%**	44%	0%	0%	11%	**78%**	11%	0%	33%	44%	22%	0%
Rating-scale: Available statistical tools for signal detection (always adequate…often very inadequate)	**67%**	22%	11%	0%	22%	**56%**	22%	0%	11%	**56%**	33%	0%
Rating-scale: Time between detection of signal and reporting (publishing) (adequate … too slow)	**78%**	11%	11%	0%	0%	33%	**67%**	0%	11%	44%	44%	0%
2.3.1 International share of work in signal detection												
Rating-scale: Work that is done within your country and at the same time in other MS or on EU level (very little…very much)	**75%**	13%	13%	0%	13%	38%	**50%**	0%	13%	38%	38%	13%
Rating-scale: Use of information from other agencies (in nearly all cases…very seldom)	**50%**	**50%**	0%	0%	0%	**63%**	38%	0%	0%	**63%**	25%	13%
Number of PhVWP meetings at which one member of the agency has participated	25%	38%	38%	0%	38%	38%	25%	0%	0%	43%	29%	29%
2.4 Safety issue assessment												
2.4.1 Share of responsibilities in safety issue assessment												
Number of PSURs assessed	25%	**50%**	25%	0%	**71%**	29%	0%	0%	33%	17%	33%	17%

Number of assessment reports written per population	11%	33%	33%	22%	22%	**56%**	11%	11%	0%	25%	38%	38%
Rating-scale: National capabilities to identify and assess signals (fully available…nearly not present)	**56%**	33%	11%	0%	11%	22%	**67%**	0%	25%	0%	**63%**	13%
Rating-scale: MAHs compliance with duty to assess safety issues (very good…very bad)	**67%**	33%	0%	0%	0%	**63%**	38%	0%	13%	**50%**	25%	13%
2.4.2 Expertise for safety issue assessment												
Rating-scale: Availability of external expertise in your country for routine cases (always when necessary…very scarce)	44%	**56%**	0%	0%	22%	22%	**56%**	0%	11%	44%	44%	0%
Rating-scale: Availability of external expertise in your country for exceptional cases (always when necessary…very scarce)	**56%**	33%	11%	0%	22%	44%	33%	0%	22%	44%	33%	0%
2.5 Decision-making												
Rating-scale: Come to adequate decisions (for NAPs/MRPs/CAPs) (always…seldom)	**75%**	13%	13%	0%	25%	**50%**	13%	13%	13%	38%	38%	13%
Rating-scale: Come to decisions in good time (for NAPs/MRPs/CAPs) (always…seldom)	**50%**	38%	13%	0%	25%	**50%**	13%	13%	13%	**50%**	25%	13%
2.6 Communication/Action												
2.6.1 Timeliness of Communication/Action												
Mean time from 1st ICSR to action with respect to this safety issue (adequate … too slow)	30%	40%	20%	10%	0%	40%	40%	20%	10%	30%	**60%**	0%
Rating-scale: Time from 1st signal to action with respect to this safety issue (adequate … too slow)	**50%**	38%	13%	0%	13%	25%	**50%**	13%	13%	38%	**50%**	0%
Rating-scale: Implement decisions in good time (for NAPs/MROs/CAPs) (always…seldom)	**56%**	33%	11%	0%	0%	33%	44%	22%	11%	**56%**	22%	11%
Rating-scale: Reaching targets for timing of communications (very good…very bad)	40%	**50%**	10%	0%	10%	30%	**50%**	10%	20%	20%	**60%**	0%
2.6.2 Comprehensiveness of Communication/Action												
Number of information events for HCPs with participation of agency	40%	40%	20%	0%	**60%**	40%	0%	0%	10%	40%	**50%**	0%
Number of responses to inquiries by HCPs	40%	**50%**	10%	0%	**70%**	10%	20%	0%	0%	**70%**	30%	0%
Number of letters to MAHs to amend SPCs	30%	40%	30%	0%	**70%**	30%	0%	0%	20%	30%	**50%**	0%
Number of variations evaluated	22%	**67%**	11%	0%	**56%**	33%	11%	0%	11%	33%	**56%**	0%
Number of answers to CHMP	33%	44%	22%	0%	44%	**56%**	0%	0%	22%	33%	33%	11%
Number of bulletins issued	30%	30%	40%	0%	**70%**	30%	0%	0%	20%	20%	**50%**	10%
Number of other answered queries	20%	20%	**50%**	10%	**60%**	0%	40%	0%	20%	10%	**50%**	20%

Number of inspections of MAHs carried out where PhV was an issue (at least partially; including inspections that were carried out by other authorities in the coutry)	**60%**	10%	30%	0%	**80%**	10%	10%	0%	25%	38%	38%	0%
Rating-scale: Reached all relevant stakeholders (always…seldom)	33%	44%	22%	0%	22%	33%	44%	0%	0%	**50%**	**50%**	0%
Rating-scale: Consistency of communication across stakeholders (incl. MAHs) (very good…very bad)	30%	**50%**	20%	0%	20%	30%	**50%**	0%	0%	44%	**56%**	0%
Rating-scale: Consistency of communication across NCAs and EMEA (very good…very bad)	44%	44%	11%	0%	10%	40%	40%	10%	0%	44%	44%	11%
2.7 General factors												
2.7.1 Amount of work done												
% of work acting for the Community (as Rapporteur)	44%	22%	22%	11%	33%	33%	33%	0%	11%	22%	**56%**	11%
% of work acting for the Community (as Reference Member State)	44%	22%	22%	11%	33%	33%	33%	0%	11%	33%	44%	11%
% of work acting on a nationally licensed product	44%	11%	33%	11%	33%	33%	11%	22%	11%	33%	33%	22%
Number of documents prepared (legal acts, quidelines)	40%	10%	40%	10%	**60%**	20%	10%	10%	20%	40%	20%	20%
Number of scientific publications with at least one author from the agency in last year	20%	40%	40%	0%	**70%**	30%	0%	0%	10%	40%	40%	10%
2.7.2 Realised timing of work												
Rating-scale: Compliance of agency with dates/requirements (very good…bad)	**70%**	20%	10%	0%	**50%**	40%	10%	0%	30%	**60%**	10%	0%
Rating-scale: Meeting general targets for timing (very good…very bad)	**60%**	40%	0%	0%	40%	40%	20%	0%	30%	**60%**	10%	0%
Rating-scale: Compliance of MAHs with 15 days (very bad…very good)	**60%**	20%	20%	0%	**50%**	30%	20%	0%	20%	**70%**	10%	0%
2.7.3 Cooperation												
Rating-scale: Compliance of MAHs with legal requirements (very bad…very good)	**50%**	20%	30%	0%	30%	40%	30%	0%	10%	**70%**	20%	0%
Rating-scale: Cooperation with MAHs (very bad…very good)	20%	30%	**50%**	0%	10%	40%	30%	20%	0%	**70%**	10%	20%
Rating-scale: Cooperation with HCPs (very bad…very good)	30%	20%	**50%**	0%	20%	30%	20%	30%	10%	**50%**	10%	30%
Rating-scale: Collaboration between NCAs and EMEA (very bad…very good)	40%	40%	20%	0%	20%	40%	30%	10%	10%	**60%**	20%	10%
Number of documents sent through EudraNet (RAS, NUIS, others) by sender, concerned MS, issue, channels	10%	30%	**50%**	10%	**60%**	0%	40%	0%	20%	30%	30%	20%
Number of regular meetings with external experts	10%	**50%**	40%	0%	**50%**	**50%**	0%	0%	10%	30%	40%	20%
Number of irregular consultations with external experts	10%	40%	**50%**	0%	**50%**	40%	10%	0%	10%	30%	40%	20%
2.7.4 Quality management												

% of staff trained per year	40%	**60%**	0%	0%	**50%**	**50%**	0%	0%	30%	**50%**	20%	0%
Number of training measures (internal or external) with at least one participant from the agency	30%	40%	30%	0%	**50%**	40%	10%	0%	40%	20%	40%	0%
3. … for the impacts/outcomes												
3.1 Impact of communications/actions												
Number of ICSRs from your country before vs. after communication	**50%**	40%	10%	0%	**50%**	40%	10%	0%	20%	**50%**	30%	0%
Total reporting rate per million inhabitants in 2004	**50%**	40%	10%	0%	**56%**	44%	0%	0%	20%	**80%**	0%	0%
Reporting rate in children per million inhabitants in 2004	**50%**	40%	10%	0%	**56%**	33%	11%	0%	20%	**80%**	0%	0%
Satisfaction of health care givers, patient groups, prescribers with the work of the agency (survey in these groups)	**50%**	20%	30%	0%	10%	30%	**50%**	10%	10%	**70%**	20%	0%
Satisfaction of prescribers with information (survey in these groups)	**50%**	40%	10%	0%	10%	30%	**50%**	10%	10%	**50%**	40%	0%
Number of market withdrawals of drugs (compared to other countries)	20%	30%	**50%**	0%	**80%**	10%	10%	0%	20%	30%	**50%**	0%
Number of suspensions of marketing authorisation	20%	40%	40%	0%	**70%**	20%	10%	0%	20%	40%	40%	0%
Number of dear doctor letters sent	10%	**60%**	30%	0%	**80%**	10%	10%	0%	0%	30%	**70%**	0%
Number of changes in SPCs made	20%	**50%**	30%	0%	**60%**	10%	30%	0%	10%	40%	**50%**	0%
Number of applications for variations adopted/refused	10%	**50%**	40%	0%	**50%**	30%	20%	0%	0%	**60%**	40%	0%
Number of variations not validated	0%	25%	**75%**	0%	**63%**	25%	13%	0%	0%	38%	**50%**	13%
Statistics on use of agency's web services	22%	44%	22%	11%	**78%**	22%	0%	0%	22%	22%	33%	22%
3.2 Outcomes												
Incidence of ADR-relevant diseases	**70%**	20%	10%	0%	10%	30%	40%	20%	20%	**50%**	30%	0%
Hospitalisations due to ADR	**70%**	20%	10%	0%	10%	40%	**50%**	0%	10%	**70%**	20%	0%
Mortality due to ADR	**70%**	20%	10%	0%	10%	20%	**70%**	0%	10%	**70%**	20%	0%
Number of quality-adjusted life years lost due to ADRs	**50%**	40%	10%	0%	0%	0%	**80%**	20%	10%	**50%**	40%	0%
Potential years of life lost due to Adverse effects from medicines	30%	**60%**	10%	0%	0%	10%	**50%**	40%	0%	**50%**	40%	10%
Changes in consumption data	**50%**	20%	30%	0%	20%	20%	**60%**	0%	10%	40%	**50%**	0%
(Change in) Prescription data (controlled for population parameters)	40%	40%	20%	0%	30%	0%	**70%**	0%	10%	30%	**60%**	0%