EUROPEAN COMMISSION
ENTERPRISE AND INDUSTRY DIRECTORATE-GENERAL

Consumer goods
Pharmaceuticals

Brussels,
February 2007

Subject: Assessment of the Community System of Pharmacovigilance – European Commission Public Consultation - presentation of results

1. INTRODUCTION

The services of the European Commission have been in dialogue with the scientific and policy committees of the European regulatory system as well as the Heads of Medicines Agencies – Human and its European Risk Management Strategy Facilitation Group (ERMS-FG) regarding the Commission examination of the EEA pharmacovigilance system entitled 'Assessment of the Community System of Pharmacovigilance'. Following advice from the Committees, the European Commission conducted a public consultation in 2006 and this paper presents the results of that consultation.

2. BACKGROUND

In January 2004, the Commission presented to the Pharmaceutical Committee a proposal for an Assessment of the Community System of Human Pharmacovigilance. The proposed Assessment was justified on the basis of new pharmaceutical legislation, enlargement of the EU and the changing expectations of our stakeholders. Furthermore, the Commission argued that it was our shared responsibility to ensure our public health protection mechanisms continue to be robust. The proposal had three phases:

- an assessment of the current system including site visits to the national competent authorities and the EMEA,
- identification of strengths and weaknesses, and
- proposals on how the system might be strengthened.

Following the Pharmaceutical Committee the Commission issued a call for tender and following review of the bids the contract for the Assessment was awarded in December 2004 to a joint bid from "Fraunhofer Institute Systems and Innovation Research" and "Coordination Centre for Clinical Studies at the University of Tubingen" (KKSUKT).

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The Commission wrote to the Heads of Agencies in December 2004 notifying of the contract being awarded and requesting support with site visits. Presentations on the Assessment were provided at the Heads of Medicines Agencies-Human (HMA-H) meetings. The HMA-H agreed that its European Risk Management Strategy Facilitation Group (ERMS FG) would provide regulatory advice to the contractors and that the data from the existing ERMS survey on pharmacovigilance resources could be released to the contractor.

By 10 June 2005 the contractors had visited the 27 agencies making up the EU network of pharmacovigilance. This comprises each of the national agencies (two for Germany) plus the EMEA. On 15 June a workshop was held by the contractors at which stakeholders attended together with members of the ERMS group. The workshop aimed at reviewing the initial results of the study, to discuss key aspects of the Community system and to shape possible recommendations put forward by the contractors to strengthen the system. Also in June the ERMS group, after seeking confirmation of approval from HMA provided the contractors with the results from the ERMS survey of pharmacovigilance resource in the EU. During the summer and early autumn of 2005 the contractors conducted a written survey, which took into account the existing ERMS survey results, as well as, the pharmacovigilance elements in the HMA bench-marking exercise. The ERMS FG offered advice on the details of the survey.

Regarding the results, the draft final report was received by the Commission on 16 November 2005 and the results were discussed at the Pharmaceutical Committee, the Heads of Medicines Agencies and its ERMS-FG and the Commission consulted the Committee on Human Medicinal Products (CHMP) and the Pharmacovigilance Working Party on the handling strategy. The public consultation document was finalised with input from these Committees as well as the Pharmaceutical Committee.

The Commission public consultation entitled “Assessment of the Community System of Pharmacovigilance” was announced at the EuroDIA meeting in February 2006 and was formally launched on 16 March 2006. Dialogue has been maintained with the committees during the conduct of the consultation and its analysis.

3. THE CONSULTATION

Interested parties were invited to submit their comments between 16 March 2006 and 12 May 2006 (although late responses were accepted up to July 2006). To facilitate the public consultation the Commission held two workshops in April 2006 at its offices in Brussels. On 20 April 2006 a workshop was held with healthcare professional and patient groups and the meeting was also attended by a representative of a thalidomide victim association. On 21 April 2006 a workshop was held with industry groups.

4. CONTRIBUTERS

The Commission consultation received 48 contributions.

In summary:

- 7 responses from patient, consumer and victim groups

- 10 from healthcare professional groups of which 4 represented doctors, 3 pharmacists and one nurses
- 16 from industry including all the relevant European Industry Associations
- 10 from regulators including the European Medicines Agency Committees and individual medicines agencies
- 5 others, including the WHO Uppsala Monitoring Centre and the International Society for Pharmacoepidemiology

List of those providing a written contribution to the public consultation

To aid analysis, where joint responses were received from more than one organisation falling within the same stakeholder group these responses were counted only once. In contrast, if joint responses were received from organisations falling within different stakeholder groups these were counted separately.

In the list of individual responses provided below the number corresponds to the numbers listed against specific comments in Annex 1.

Patients, consumers and victims (7)

1. Thalidomide UK

2. European Patients' Forum

3. European AIDS Treatment Group (EATG)

4. European Cancer Patient Coalition

5. European Federation of Allergy and Airway Diseases Patients' Associations (EFA) – joint response with IPCRG

6. Danish Consumer Council

7. Health Action International - Europe

Healthcare professionals (10)

8. European Union Geriatric Medicine Society (EUGMS)

9. International Primary Care Respiratory Group (IPCRG – primary care doctors) – Joint response with European Federation of Allergy and Airway Diseases Patients' Associations -EFA

10. Standing Committee of European Doctors (CPME)

11. European Society for Medical Oncology (ESMO)

12. Pharmaceutical Group of the European Union (PGEU - Community Pharmacists) joint with EuroPharm Forum (pharmacists + WHO European Office) and FIP (International Pharmaceutical Federation - pharmacists)

13. European Federation of Nursing Associations (EFN)

14. Professor Pascal Demoly, University Hospital of Montpellier

15. Joanne Barnes Associate Professor in Herbal Medicines, School of Pharmacy, University of Auckland

16. Prof. Dr. Joerg Hasford, Department of Medical Informatics, Biometry and Epidemiology, University of Munich.

17. Maria Judith Marquez Pradera, healthcare professional and medical advisor for the pharmaceutical industry

Industry (16)

18. AESGP – Association of the European Self-Medication Industry

19. EFPIA – European Federation of Pharmaceutical Industries and Associations

20. EGA – European Generic Medicines Association

21. IFAH-Europe – International Federation for Animal Health Europe

22. EuropaBio

23. GIRP – European Association of Pharmaceutical Full-Line Wholesalers

24. PPTA-Europe (Plasma Protein Therapeutics Association)

25. LIF – The Danish Association of the Pharmaceutical Industry

26. BAH - Bundesverband der Arzneimittel-Hersteller e.V. (German proprietary medicines manufacturers association)

27. BPI – Bundesverband der Pharmazeutischen Industrie (German Pharmaceutical Industry Association)

28. GlaxoSmithkline

29. Rottapharm Itali and Delta Laboratories

30. Dr Wolfgang Matthies, Ecolab Deutschland

31. Dr Brian Edwards, Janssen Cilag Ltd

32. EU PhRMA Pharmacovigilance Working Group

33. Voisin Consulting

Regulators (10)

34. European Medicines Agency (EMEA)

35.EMEA Committee on Human Medicinal Products (CHMP) and CHMP Pharmacovigilance Working Party (PhVWP)

36. CHMP Pharmacovigilance Working Party (PhVWP)

37. EMEA Committee for Herbal Medicinal Products

38.EMEA/CHMP Working Group with Patient Organisations (report of March 2005 provided by Dr Priya Bahri of the EMEA)

39. The Danish Medicines Agency

40. The Dutch Ministry of Health, Welfare and Sport

41. Swedish Medical Products Agency

42.Abdelkader Helali, Director, Centre National de Pharmacovigilance et de Materiovigilance

43. Dr Priya Bahri of the EMEA

Others (5)

44. International Society for Pharmacoepidemiology

45. An ad-hoc group of ten pharmacoepidemiologists

46. Professor Saad Shakir, Director, Drug Safety Research Unit, UK

47. WHO Collaborating Centre for International Drug Monitoring

48. La revue Prescrire

The individual responses will be placed on the web at the following web address: http://ec.europa.eu/enterprise/pharmaceuticals/pharmacovigilance_acs/index.htm.

5. OVERVIEW OF COMMENTS RECEIVED

In addition to the individual responses being posted on the web, Annex 1 provides a detailed breakdown of the individual comments received from the forty-eight contributors to the consultation. In this section a high level summary of the key consultation messages is provided.

Legal framework and its implementation

The vast majority of responses call for a **change to the legal framework for pharmacovigilance** in the EU, either explicitly or by requesting changes to the system

which could only be realised through a change to EU law. The pharmaceutical industry makes a strong **call for rationalisation of the legal framework** calling the **current legal framework contradictory, confusing, unclear and complex**. The fact that the different Member States have slightly different rules, including requirements going beyond those in EU legislation is highlighted, including the cost implications of these differences and the fact that this **interferes with the operation of the European single market** and the free movement of goods. The lack of harmonisation is suggested to be **detrimental to public health** as it diverts resources away from safety monitoring towards meeting disparate administrative requirements. While the European industry associations representing the innovative industry and biotechnology industry together with the German pharmaceutical industry association and a major European innovative company explicitly call for **a single Council regulation on pharmacovigilance to replace all existing EU laws**, the European association representing the non-prescription industry calls for a period of stability with harmonisation at the level of EU guidance (despite the fact that this might contradict EU and National law). Additional comments on the legal framework include a **need for better regulation** and a call from the European regulators (the Committee on Human Medicinal Products and its Pharmacovigilance Working Party) for a change of legislation on periodic safety update reports (PSURs), renewals, **clear legal roles, responsibilities and accountability** and notifications of major drug safety announcements. Both the industry and regulators call for the **pharmacovigilance system to be strengthened**.

The consultation was conducted in parallel with a consultation on the main EU guideline on pharmacovigilance: Volume 9a of Eudralex. Perhaps because of this, a number of comments on implementation focussed on Volume 9a including the fact that it only exists in English, that some provisions were unclear and others of questionable legal basis and enforceability. Further comments suggested that a comparison of the divergent requirements in the Member States should be conducted and made public. There is a call for the pharmacovigilance **requirements placed on industry to be determined by the level of knowledge about the drug** i.e. not having the same requirements for all products.

Resources

There is a strong call, particularly from the regulators and academia for **increased resources in pharmacovigilance**. This includes funding and experienced staff for regulatory pharmacovigilance, as well as funding of research into the **methodologies of pharmacovigilance, epidemiological studies, drug safety communication and audit** (both quality management and outcome monitoring). There was a particularly **strong call for more public funding** with a small number of responders calling for funding to be entirely public. A call for funding from the **European Commission Framework Programmes** was clear particularly from the regulators. A strong message from industry, regulators and academia is that current **duplicative reporting requirements lead to wasted resources and inefficiency.**

Organisation of the pharmacovigilance system

In terms of organisation within the EU, divers but potentially complimentary messages come from the consultation. While there is a clear call for **harmonisation** of requirements in the Member States, there are calls for more regional centres, centres of excellence, a focus on the overall EU system rather than disparate Member State systems with **only one procedure in Europe** and a clear message, particularly from the regulators, that the **Member States have a crucial role to play** in the conduct of pharmacovigilance.

A small number of responders call for **greater collaboration with international partners** including the World Health Organisation and non-EU drug regulators. Three responders suggest that medicines **regulation and industry competitiveness should be split** at the level of the European Commission. Additionally responders suggest that within the regulatory agencies the **authorisation of medicines should be split from pharmacovigilance** to ensure that decision-making on safety issues is independent.

Transparency and stakeholders

Sixteen responders explicitly commented on transparency, with all **calling for increased transparency**. These calls for increased transparency related to all steps in the pharmacovigilance process and related to both pharmacovigilance data and documents relating to decision making. These calls came from all stakeholder groups (although most strongly from patients, consumers and regulators).

European patient groups in particular but also some health professional groups and regulators call for **increased collaboration between stakeholders**, particularly **engagement with patient groups**. The key role of pharmacists and the need to work with academia were also highlighted.

Roles, responsibilities, inspections and compliance

EU legislation requires a marketing authorisation holder (a company holding a licence for a medicine) to have a "**qualified person" for pharmacovigilance**. While the regulators call for a change whereby the qualified person would be identified with a corporate entity, some sections of the industry call for flexibility. A specific suggestion is that **the supervisory authorities for pharmacovigilance**, currently defined in EU legislation as the Member State where the manufacturing authorisation is issued, should in fact **be the Member State where the qualified person resides**.

Patient groups, regulators and some industry associations call for a **greater focus on industry compliance including inspections** (and establish clear standards for inspections). Regulators and academia call for **greater regulatory power over industry in the post-authorisation period** (e.g. the **power to force companies to conduct studies** and stronger powers in case of non-compliance).

Current legislation requires industry to submit a detailed description of its pharmacovigilance system with each marketing authorisation application. The law then requires any change to be via a variation to the marketing authorisation (which requires

an application and regulatory approval). European industry and regulators suggest that scrutiny of industry systems should remain but bureaucratic burden should be reduced by **establishing a new legal concept the "pharmacovigilance system master file**" which would be maintained by companies, submitted on request and **subject to inspections**.

An suggestion from academia is to create a requirement for all clinical trial results to be scrutinised by the regulators in the post-authorisation period.

Adverse Drug Reaction (ADR) reporting

Eleven consultation responses **explicitly call for the introduction of consumer reporting** of ADRs (which is currently excluded by legislation). This call comes from European patient and consumer groups as well as some regulators, industry, academia and the World Health Organisation.

Thirteen consultation responses including **all the main European industry associations**, as well as, some regulators, academia and patients **call for a rationalisation and simplification of the ADR reporting requirements for industry and regulators** (that are currently dictated by EU law). They point out that there is enormous duplication of effort with a single report circulating between numerous senders and receivers. The perceived **waste of resource** is highlighted, as well as the fact that the resource could be **reallocated to better public health protection**. The role of the European pharmacovigilance database "**Eudravigilance" is highlighted** as being key to the rationalisation and simplification of the system. Eleven responses explicitly call for **all ADR reports to be submitted to one single point, that being Eudravigilance**. No responders argue for maintaining the current multiple reporting.

The **costs of electronic reporting** particularly for small and medium sized enterprises are highlighted by a number of industry responses and one of the suggested solutions is to have one set of standards applicable across the EU. The **duplication of effort and administrative burden of reporting ADRs published in the literature is highlighted**. The fact that all marketing authorisation holders have the same requirement for reporting cases published in the literature, leading to hundreds of duplicate reports being submitted, leads the industry associations to call for rationalisation of the requirements.

Numerous suggestions are made on how **ADR reporting** from healthcare professionals and patients could be **stimulated** including ways to facilitate reporting such as internet and telephone reporting and having consumer reporting forms or reminders on patient information leaflets.

Other data sources

European patient groups, academia, European regulators and the World Health Organisation are all calling for greater use of more robust data sources rather than relaying mainly on spontaneously reported suspected ADR reports ("**move up the evidence hierarchy**"). Specifically there is a **strong call** for a dramatic **increase in the number of post-authorisation safety studies**, both those conducted by industry and independent academic studies. Regulators and academia call for such studies to be

mandatory while patient and consumer groups call for **stronger regulation of non-interventional studies**.

Industry, regulators and academia call for **investment into databases and other data sources** that can be used **for pharmacoepidemiological studies**, together with increased training in pharmacoepidemiology and networking of academics in Europe (to increase capacity and exchange best practice).

The bureaucratic burden and **waste of resources for both industry and regulators** of the current requirements for **Periodic Safety Update Reporting** are highlighted by industry, regulators and academia. Responders call for rationalisation of the reporting with a **clear legal basis for work sharing** by both industry and the regulatory authorities.

Data management and safety issue detection

Industry and regulators call for **full utilisation of Eudravigilance**, the European pharmacovigilance database, **including financial and human resource investment**.

Patients, academics, regulators, industry associations and the World Health Organisation call for routine use of statistical methodologies in signal detection, including international collaboration.

Assessment and decision-making

Industry and academia call for the power to **compel industry to conduct post-authorisation safety studies**, in the event that a safety issue is detected or suspected.

There is cross-sector support for **patient involvement in decision-making** with additional calls for involvement of victims of adverse reactions, healthcare professionals and industry. There is a clear call for routine use of external experts and of peer-review.

With respect to the **European referral system** there is a clear message from across the stakeholder groups that there should be **rationalisation of the system** with fast, streamlined, legally binding decisions and focussed, rational input from the affected industry. The industry particularly emphasises the need for **more European rather than divergent Member State decisions** on drug safety issues.

Regulatory action, risk minimisation and risk management

Risk management plans are highlighted as **key** tools in pharmacovigilance although the regulators stress the **need for a legal requirement that companies complete the data collection** specified in plans.

The European Medicines Agency calls for a new simple system whereby generic companies would have to follow the innovator when changes to product information relevant to the safety of products need to be implemented.

Patient groups call for **new products to be labelled as such** for their first two-years on the market so that patients can make informed choices. Such a system could also be used to stimulate reporting of suspected ADR with new products.

Education and decision-support for prescribers, dispensers and users of medicines is a strong theme of many consultation responses. Many call for **integration of drug safety information into prescribing and dispensing systems,** while others call for education about reporting suspected adverse reactions. The need for **funding** is highlighted.

Communication

Patients, industry and regulators call for **greater European harmonisation and coordination of drug safety communications.** The regulators call for a strong **legal requirement for the industry to have to inform regulators prior to making major safety announcements**, such as product withdrawals. Industry calls for clear contact points with the regulatory authorities ideally with one contact per authority.

Various responses stress the importance of getting quality information on important drug safety issues to the various stakeholders in a timely manner. Amongst these are specific practical suggestions which could improve the system. **A stakeholder partnership / forum on drug safety communication** is proposed.

Outcome of regulatory action and quality management

A strong message from across the stakeholder groups is the **need to routinely monitor the outcome of regulatory action** to ensure that public health has been adequately protected / promoted. The need for outcome monitoring to be a **legal requirement,** as well as, the need for it to be **resourced** is highlighted.

All stakeholder groups call for **quality management in pharmacovigilance** with clear standards ("**Good Pharmacovigilance Practice**") and **routine audit**. The link to improved public health is highlighted.

Pharmacovigilance for herbal medicinal products

The European Medicines Agency's committee for herbal medicinal products, as well as one academic working in herbal safety have provided important consultation responses which highlight the need for robust pharmacovigilance for herbal medicines and the peculiarities of herbal medicines including how they are sold and used. The **need for guidance on herbal pharmacovigilance** is one important recommendation made.

6. CONCLUSIONS

The Commission consultation "Assessment of the Community System of Pharmacovigilance" received 48 written responses representing the views of the

spectrum of stakeholders. Compelling arguments are provided that the current system is complex and that there is a need for more and better use of resources with reduction in duplicated effort with simplification of reporting requirements, both single case reporting and periodic reporting and clearer roles, responsibilities and standards. **There is a strong and clear demand from all stakeholder groups for the Community pharmacovigilance system to be strengthened and rationalised.**

European Commission,

February 2007.

Annex 1: Detailed analysis of individual comments

Details of the responses

The responses from the different contributors have been analysed and broken down into the following categories:

Legal framework and its implementation

Rationalise the law

We need better regulation in EU pharmacovigilance (19)

The legal framework needs to be improved (19, 22)

There is a need for a new approach (19)

The current procedures are contradictory and unclear. (19, 22, 28)

The current rules are complex (and confusing). (19, 20, 22, 25, 28, 29, 33)

One Council pharmacovigilance regulation is required which provides clear procedures and roles and responsibilities. (19, 22, 27, 28)

The legal framework and its implementation should be fully harmonised between Member States. (3, 20, 22, 27, 33)

One set of rules should cover the Member States and be legally binding (19, 20, 27, 29).

Prohibit additional Member State requirements beyond the EU ones (19, 20, 27, 29).

New legislation would lead to a period of uncertainty (18)

We do not support change to legislation (18, 33).

We need all legal texts in one place (33, 41)

There is a need for a change of legislation on PSURs, renewals and regarding notification of major drug safety announcements (35).

Implementation

Focus on better implementation of the legal framework (12, 18, 33, 41).

There is a need for user guides in pharmacovigilance (33)

Volume 9 could be improved / has ambiguous provisions (18, 19, 27)

Volume 9 is only in English / should be in all EU languages (19, 27)

New requirements in Volume 9 are of unclear legitimacy (19)

Guidelines will need updating in light of the new legislation and the experience gained with it (35).

There is a need for publication of a comparison / map of EU vs. national rules in pharmacovigilance (22, 33).

Other

Bureaucracy should be reduced (16, 20, 27)

Need to rationalise the system (20, 22)

Need to strengthen the system (20, 21, 35, 39)

Need to assess the impact of current methodologies e.g. PSURs (16, 46)

There is a need for simplification (22, 33).

Rationalise and simplify pre and post-authorisation requirements (19, 27)

There is a need for greater harmony in the conduct of pharmacovigilance across Europe. (1, 19)

There is a need for the same robust pharmacovigilance whatever the authorisation route (12).

There is a need for clearer roles and responsibilities in pharmacovigilance (and this may require legal changes) (19, 34, 35)

New legal provisions are required that clarify accountability (35).

Resources

Amount

Resources for pharmacovigilance are inadequate / need to be increased (16, 33, 35, 36, 41)

Resources at many Member State agencies are inadequate. (7, 33)

Resources for pharmacovigilance education need to increase (35, 36).

There is a need for increased resources in pharmacoepidemiology. (35, 36, 44, 46)

There is a need for increased public funding of individual pharmacoepidemiological studies. (34, 35, 36, 44, 47, 48)

There should be public funding for independent research and research centres (16, 34, 36, 44, 45)

We should fund research into the methodologies of pharmacovigilance and pharmacoepidemiology (35, 39, 46)

Specific support is needed for epidemiological studies on vaccines. (34)

There is a need to fund research into the methodologies used to minimise risk (16, 35, 46)

Risk management planning needs to be adequately resourced (35).

There should be greater use and funding of regional centres for pharmacovigilance. (34, 48)

There is a need for major investment into better communication about medicines safety (16, 19, 22, 35, 36, 38, 40, 41, 47)

The pharmacovigilance system needs audit and this need funding (2, 5, 9, 19, 36, 38, 47, 48)

Source

Pharmacovigilance must receive adequate public funding (35, 36, 48)

Pharmacovigilance should be totally publicly funded (42, 48)

Pharmacovigilance in regulatory authorities should not be funded by the industry (48)

Public, private partnerships should be considered to fund drug safety studies (2, 34, 35)

Pharmacovigilance should be included in the VIIth framework programme. (34, 35)

Efficiency and organisation

Optimise use of resources, avoiding duplication and inefficiency. (19, 20, 29, 33, 34, 35, 36, 46).

Duplicative reporting requirements impose a big cost on small and medium sized enterprises (29, 33).

Twenty-four hour pharmacovigilance cover is of questionable cost benefit (41)

Resource from spontaneous reporting should be redeployed to other aspects of pharmacovigilance such as risk assessment, minimisation and communication. (19, 29, 33, 34, 44, 46)

Resource from PSURs should be redeployed to other aspects of pharmacovigilance such as risk assessment, minimisation and communication. (46)

Other

A precise assessment of European pharmacovigilance resource needs should be conducted. (34)

There is a need for experienced professionals in the competent authorities pharmacovigilance departments (12, 33, 35, 36).

Each Member State should have an English-speaking contact point (33).

One should create a European list of experts to support the system (and the Member States) (22, 33).

Organisation

EU / Member State organisation

Member States must harmonise in pharmacovigilance (29, 33)

The focus should be on the overall European system and not duplicative Member State systems. (7, 19, 22, 27)

We support a "centres of excellence" model for the conduct of specific tasks (41).

We should use regional pharmacovigilance centres more (34, 41, 48)

Member States have a central role in the conduct of pharmacovigilance. (7, 35, 36)

One assessment only per procedure in Europe – no duplication between Member States (19, 22, 27, 29)

International

Greater networking between international agencies is required with early safety warnings (39, 47)

Need to finalise confidentiality arrangements with non-EU countries to allow pharmacovigilance information to be exchanged (39).

Greater international harmonisation through ICH would be helpful (20)

The EMEA / Eudravigilance duplicates much of the work of the WHO-Uppsala Monitoring Centre – there is a need for closer collaboration (35, 47)

Splitting tasks

Because of conflict of interest within the European Commission DG Enterprise and Industry should not be responsible for drug regulation. (7)

Drug regulation and industry sponsorship should be split. (7)

DG Health and Consumer protection (Sanco) should be responsible for pharmacovigilance. (7, 45)

Regulation should be separate from the industry. (7, 48)

Organisationally, authorisation of medicines should be split from pharmacovigilance; (7, 42)

A new European Pharmacovigilance Committee should be established autonomous from the CHMP (48)

Safety studies should be independent from the industry. (6, 7)

Other

Member State competent authorities should be trainers in pharmacovigilance (following the WHO model) (35, 41).

There is a need for clearer rules on outsourcing (33).

Transparency and stakeholders

Transparency

We need a greater level of transparency (at all steps in the pharmacovigilance process) (2, 7, 16, 22, 35, 38, 46, 47, 48)

All decisions should be clearly motivated and should be published (38, 47, 48)

European assessment reports should be made public (41, 48)

Patients / consumers / the public should have access to ADR data (2, 16, 38, 48)

Data on drug consumption should be made public (48)

Periodic Safety Update Reports should be made public (6, 40, 48)

Periodic Safety Update Report conclusions should be recorded in product information (47)

Periodic Safety Update Report assessment reports should be made public (20)

Risk Management Plans should be made public (45)

Patient confidentiality should be respected (5, 6, 9)

Transparency needed on post-authorisation commitments of the industry (38).

Stakeholders

Patients / consumers

There should be investment in capacity building for patient groups. (3)

Patients' rights should be strengthened. (13)

Each Member State should set up a working group with patient organisations (38)

Close cooperation with patient safety alliances is needed (16).

Patients / consumers should be consulted prior to communicating. (2, 3, 38)

Patient organisations / learned societies could facilitate information campaigns about pharmacovigilance. (2, 11, 12, 38)

Enhance links between patient organisations and industry so that confidential information can be shared. (3)

Pharmacists

Systematically involve pharmacists in pharmacovigilance in all Member states (12)

Community pharmacists are committed to contributing to health protection through pharmacovigilance (12).

Pharmacists are uniquely placed to give messages on the safe use of medicines (12).

Academia

There should be closer collaboration between authorities and academia including staff rotation (16)

There is a need for greater coordination with academia / better harness the resources of academia (20, 36)

Other

There needs to be engagement between regulator and patients and healthcare professionals (35).

Roles, responsibilities, inspections and compliance

Qualified person and the supervisory authority

The qualified person in pharmacovigilance should be identified with a corporate identity leading to one pharmacovigilance system per company with one qualified person responsible for the system. (34)

The qualified person role needs to be clear and flexible, including the role of the deputy (19, 27, 28).

Create a supervisory authority for the pharmacovigilance system i.e. the member state where the qualified person for pharmacovigilance is located. (34)

Compliance and enforcement

There is a need for new tools for non-compliance e.g. suspend the marketing authorisation. (34)

Greater focus is needed on measuring industry compliance including inspections. (3, 5, 7, 9, 48)

Industry compliance should be routinely monitored (including inspections) (12, 19, 20, 35, 38, 41)

Monitoring of industry compliance requires increased resources at the authorities (35).

Give regulators greater enforcement powers in case of industry non-compliance (45, 48)

Regulators need more powers over industry post-authorisation (35, 36, 40, 44)

Description of the system

Establish a legal basis for the "Pharmacovigilance System Master File" / "Summary of Pharmacovigilance System" which would describe the companies system and not be product specific. This would be maintained on site by the qualified person. (20, 34)

Regarding the description of the pharmacovigilance – this should be required only once per company per category of products (18)

Inspections

Establish clear EU standards for inspections. (19, 28)

Need greater EU coordination of inspections (19, 20)

Other

There is a need to create a culture of safety involving all stakeholders based on guiding principles of safety in pharmaceuticals. (31)

Industry is responsible for the safety of its products (including assessing benefit risk balance) (20, 39)

Regulators should be responsible for scrutinising all clinical trial data (45)

Regulators should be advocates for patients not industry (48)

Need to consider the interface with financial legislation (19)

Need clarity on the requirements for pharmacovigilance training within the industry (19)

Industry must notify potential changes to the benefit risk balance of its products (need for a stakeholder dialogue) (39)

Some Member States do not notify all MAHs of ADR reports received (20)

Data sources and collection – ADR reporting

Consumers / stakeholders

Spontaneous ADR reporting needs to be embedded in local healthcare systems. (35, 36)

Introduce consumer reporting. (2, 5, 6, 7, 9, 13, 22, 34, 37, 46, 47, 48)

Need to assess the utility of consumer reporting (18, 35, 38, 39)

Consumers should be reminded to report adverse drug reactions to their healthcare professionals (12, 38).

Involve patient organisations and / or learned societies in ADR reporting. (2, 11, 20)

Pharmacists are key professionals for ADR reporting (12).

Stimulating reporting

Member States should continue to encourage reporting (35, 40)

Make ADR reporting compulsory. (2, 13)

Do not pay reporters. (13)

Stimulate healthcare professionals to report via CME etc, via requirement to have report to get jobs, provide feedback to reporters (17, 20, 38)

Make / confirm that reporting is blame free. (2, 3, 13, 35, 40)

Consider whether confidentiality issues deter reporting (35).

Better information exchange between doctors and pharmacists (e.g. on what product what dispensed) will improve ADR reporting (12).

Other

The definition of adverse drug reaction should be amended to make it independent of dose (43)

ADR reporting is important (35, 46)

An intensive monitoring scheme / list is required in Europe (20, 46, 48)

Reporting requirements

Simplify the reporting requirements to a single point in the EU – single EU report - (increase efficiency and build on Eudravigilance). (3, 8, 18, 19, 20, 22, 25, 33, 34, 44, 46)

Simplify the reporting requirements for non-EU cases to a single point in the EU (increase efficiency and build on Eudravigilance). (18, 19, 20, 27)

Simplify reporting to all serious suspected non-EU ADRs. (19, 20, 28, 34, 40)

For mutual recognition products reporting can be simplified to the Member State where the reaction occurred and Eudravigilance (40).

Harmonise reporting methods across the EU (35)

Waive electronic reporting requirements for small companies (30)

All ADRs and all concerns of patients should be reported (47)

English only should be used for pharmacovigilance reporting (19, 20, 25)

Non-serious ADR reports should all be entered onto the Eudravigilance database (40)

Methodology of reporting

Make reporting simple, clear and quick. (3, 12, 41)

Ensure that there is no confusion between different types of reporting system (e.g. error reporting). (2, 3)

Introduce internet reporting. (2, 13, 29)

Introduce reporting via telephone hotlines. (2, 13)

Include reporting slips or reminders on Patient Information Leaflets. (2, 12)

Prescribing / dispensing software should allow automated ADR reporting (29, 41).

Software for patient records, prescribing and dispensing should prompt reporting of ADRs (12, 20, 41, 47)

Electronic standards

To reduce costs for industry facilitate sharing of E2B infrastructure (18, 27)

Reduce fees and simplify MedDRA subscription (27, 30)

EVWEB training should be organised nationally and in local languages (27)

Guidelines justifying electronic reporting are required (33).

Ensure that electronic reporting is the same / interoperable for all authorities (29, 35)

Literature reporting

Literature reporting for well-established substances should be much less frequent (18, 20, 27)

Literature should be covered by laws e.g; must report before publishing (17, 20)

Literature reporting should be conducted not by industry but by a literature agency (20)

Literature searches should be based on indication and route of administration not just drug substance (29)

Other

Focus less on increasing the volume of ADR reporting. (7)

Focus less on ADR reporting and more of data higher in the evidence hierarchy. (45, 47)

Focus on the follow up of key reports. (7)

Industry should be able to request follow up of cases via the regulators (20)

Data sources and collection – other data sources

Quality or data / information

We need to move up the evidence hierarchy (35, 39)

Focus on the quality of healthcare data used for safety studies (5, 9)

Ensure data suppliers (doctors) are adequately supported. (5, 9)

Periodic Safety Update Reports (PSURs)

PSUR submission should be reduced / rationalised (46)

PSUR submission needs coordination by substance (26, 40)

PSUR work sharing regarding bibliographic / literature cases should be introduced (18, 26, 37)

PSUR birth dates should be harmonised for all well-established substances including herbals (18, 20, 26)

Each PSUR should contain a meta-analysis of clinical trial data (41).

The substance related part of the PSUR should be submitted only once for all companies with products containing that substance (18)

Amendment of the PSUR submission cycle should be by notification not type II variation (18, 20, 26)

PSUR assessment reports should be used to establish harmonised safety information across the Member States (20)

There is a need to bring PSUR submission and renewal dates in line (renewal based on marketing date) (35, 40).

Work sharing between national competent authorities requires a clear legal basis. (34, 35, 39)

Fully implement work sharing between national competent authorities – to new fields (+/- extend to established products) (18, 20, 26, 35, 41)

Post-authorisation safety studies

Post-authorisation safety studies should be long-term. (2, 5, 9, 36)

Post-authorisation safety studies can be useful (20, 36)

The rules governing safety studies need harmonising across the Member States (20)

Phase IV study requirements need simplification (27)

Need for EU laws covering non-interventional studies (17)

Protocols for post-authorisation safety studies should be scrutinised by regulators (5, 9)

Protocols for post-authorisation safety studies should be scrutinised by data monitoring committees (5, 9)

Mandatory phase IV studies should be conducted for innovative medicines. (3, 45)

There should be greater use of large simple trials (36, 46)

There should be more large multinational phase IV studies (2, 3, 4, 5, 7, 9, 36, 46, 47)

Clinical trials

All clinical trial data should be reported to regulators. (45)

Clinical trial SUSAR reporting should be aligned with ADR reporting (and simplified) (19, 25, 27, 33, 41)

We need clearer roles and responsibilities for reporting of serious clinical trial adverse events. (34)

There is a need for mandatory clinical trials in the elderly. (8)

Registries

Need guidance and resources for health and drug registries (17, 19, 41)

Need a European inventory of registries available for interested parties (17, 41)

Epidemiology

There is a need for more pharmacoepidemiological data sources in Europe. (16, 19, 34, 35, 36, 44, 46)

There is a need for increased pharmacoepidemiological training capacity in Europe. (44, 45, 46)

Establish a network of excellence to conduct pharmacovigilance and risk management research. (34, 36, 46)

Need a community review of pharmacoepidemiology (45)

Other

Access to additional data sources e.g. disease registries, record linkage databases, should be optimised (35).

Need to collaborate with the European Centre for Disease Control on data collection (35).

Ensure pharmacovigilance for non-prescription drugs is not neglected. (3, 12, 37)

Harmonise / use the electronic patient record between the Member States. (3, 34, 35, 41)

Patient groups may be able to facilitate study recruitment and conduct (38).

The sources of safety information should be harmonised between the Member States. (3)

Optimise national databases. (3)

There should be a focus on paediatric pharmacovigilance. (4, 5, 9, 40)

There should be a focus on populations not tested in trials (12)

Focus on the level and cost of iatrogenic illness / research the burden of ADRs. (7, 45)

Utilise primary care networks for active data collection (5, 9)

Drug utilisation data should be routinely collected. (16, 19, 35, 38, 42, 45)

Data on the natural history of diseases should be collected (16, 19)

Maximise the use anonymised data for post-authorisation safety studies. (5, 9)

Off-label use should be monitored and reported. (5, 9, 40)

We need better ways of monitoring for long-term safety and delayed safety issues (16)

Pharmacy computer sources could be used for safety monitoring / link to patient records (12)

Data management and safety signal detection

Data management

There is a need to rationalise to a single European database – Eudravigilance (22)

There is a need for excellent databases for pharmacovigilance. (13, 39)

We need to better use Eudravigilance: realise its potential (19, 20, 22, 36)

Need to develop international standard set of definitions and guidance (22, 47)

Stakeholders need a better understanding of the EUs future requirements for medical terminologies to allow better collaboration (47)

There is a need for international collaboration, including WHO, in the development of standards for drug dictionaries (47).

There needs to be work to ensure the quality of data on ADR databases (35, 47)

An international database on biotechnology should be established (22).

Safety signal detection

Industry should have a central role in signal detection. (3)

Increase utilisation of automated signal detection using Eudravigilance (can be used to free-up resource across Europe). (19, 34, 35, 41)

Data mining / statistical tools should be used more / should be routine. (3, 16, 35, 41, 47)

International collaboration, including WHO-Uppsala Monitoring Centre is needed for optimal data mining (47)

Eudravigilance needs a Baysian data mining methodology to complement the 'PRR' (41).

For established products signal detection requires complete data and therefore it should fall to the regulators (20)

Routine use of Eudravigilance for signal detection needs implementation (with clear roles and responsibilities)(35, 36).

Evaluation, assessment and decision making

Evaluation and assessment

Regulators should have the power to compel the industry to do drug safety studies. (35, 40, 44, 45, 48)

There is a need to improve the methodology used for benefit risk assessment. (34)

There is a need to improve the awareness, diagnosis and prevention of drug allergy therefore a network of excellence for drug allergy should be funded. (14)

Risks and benefits of medicines should be compared to existing treatments. (2)

We should collect data in a way that allow comparison between ADRs in different Member States (16, 36)

There should be a single European evaluation of each ADR report / signal (22, 39).

There should be rationalisation of the involvement of companies (to increase efficiency) in European referrals (40).

Decision making

Involvement

Earlier / greater involvement of interested parties is required. (1, 24, 46)

Patients should be involved in decision making (3, 4, 19, 24, 46, 47)

Victim groups should be involved in decision making (1)

Healthcare professionals should be involved in decision making (1, 11, 24, 46)

Industry should be involved in decision making (19, 24)

Generic companies need to be involved in community referral procedures (20)

Quality

Decision making should be robust and objective. (16, 19, 22, 34, 46)

Use of external expertise should be optimised. (3, 11, 22, 35, 36)

Peer review of regulatory decisions should be routine (47)

Speed

The timelines for regulatory referrals should be shortened. (34, 35)

Decision making should be timely. (22, 33, 34)

Outcome

Consider a legally binding CHMP Opinion (35)

Opinions of the EMEA Pharmacovigilance Working Party that are not legally binding have not been routinely or consistently implemented (36).

Method

Interim changes to product information should be allowed while referrals are ongoing. (34)

European decision making is too complex and should be streamlined (5, 9, 22, 35, 40, 41)

There is a need for a streamlined decision making process from signal detection to regulatory action (35).

Coordination with international partners, including WHO, should be optimised. (2, 3, 19, 47, 48)

Develop SOPs for decision making with international collaboration including WHO (47)

Harmonisation

Decision making and subsequent regulatory action needs to increase in consistency (35).

Decision-making across Europe should be harmonised. (3, 5, 9, 22, 29)

There should be one European decision on each signal (22, 29)

Other

The Pharmacovigilance Working Party of the EMEA has worked well (47)

The Pharmacovigilance Working Party of the EMEA is ineffective / powerless (48)

The legal provisions for EU referrals need to be reviewed, with consideration of "light-touch referrals" (35)

An EU level crisis management plan is needed for nationally authorised products (36).

Regulatory action, risk minimisation and risk management

Risk management

Risk management plans are key to success (12, 35, 44, 46)

Need strong legal requirement to complete the data collection specified in a risk management plan within a defined time-frame (35, 36).

Risk management plans should be peer-reviewed especially with regard to study protocols (35)

Risk management planning needs to start early and be explicitly considered during the authorisation process (35).

Risk management plans should be the subject of scientific advice (35).

Risk management / minimisation should be applied to established medicines with known safety problems (46)

Risk management should be applied throughout the lifecycle of products. (12, 34, 35)

A best evidence model should be used as the basis for risk management. (34)

Product information

Simplify the implementation of product information changes by forcing generics to follow the originator. (34)

Label new products as being new for their first two-years on the market. (2, 6)

Label medicines that have a well-established safety profile. (2)

Patient Information Leaflets are key documents and should be optimised. (2, 47)

New safety information should be highlighted in the SPC / PIL (48)

Hospital patients should routinely be given patient information leaflets. (4)

Prescribing

Develop new tools to influence prescribing. (16, 19, 34)

There is a need for robust and timely drug safety information to support healthcare professional and patient decision making. (12, 22, 35, 38, 47)

Safety warnings should be integrated into prescribing and dispensing software (29, 41)

Education

Major investment in education about medicines safety is required. (19, 38, 47)

An education campaign about ADRs in the elderly is required. (8)

Education is key to reducing risk and education campaigns are required (17, 19, 35, 38, 47)

Education of doctors and pharmacists should focus on how to use medicines safely and rationally (both pre-and post-graduate) (35, 38, 42)

Education of Healthcare professionals on pharmacovigilance should be mandatory (29)

Other

Proactivity should underpin pharmacovigilance including proactive data collection. (5, 9, 34, 35, 36)

Major focus is needed on reducing avoidable ADRs (16, 46)

Integrate pharmacovigilance into healthcare systems (29, 35, 45)

There is a need to finalise the European Risk Management Strategy (39)

Develop a harmonised EU risk minimisation tool box. (34)

There should be limitation of the sale of medicines without the involvement of a health professional (12)

PSUR assessment reports should be used to establish harmonised safety information across the Member States and this should be implemented into prescribing and dispensing software (20)

Only restrict the use of products in the Member State where the ADRs occur (16)

Medicines distributors have very efficient product recall procedures that can be utilised (23)

Communication

Harmonisation and consolidation

There should be one European communication on each safety issue (22)

A single system for communicating common regulatory decisions (as well as guidance and principles) at EU level should be established (35).

There is a need to improve communication / tracking between regulatory committees (39).

Communications between Member States should be harmonised. (3)

There is a need to map the communication tools available in the Member States (41)

Role of industry / industry interface

Companies should inform Competent Authorities earlier for product withdrawals for safety reasons (simultaneous notification is inadequate) (34, 35, 40)

Industry should be able to talk to one EU regulatory contact point not one per authority (19, 20, 27)

There needs to be one contact point per Member State authority (22)

Regulators and not the industry should distribute "Dear Doctor Letters" (48)

Need clarity on industry notification of information which might influence the evaluation of the benefits and risks – including definitions of safety concerns c.f. signals and timeframes based on public health impact. (19)

Involve industry early in communication about safety issues (19)

Not all Member States make an effort to identify all MAHs (20)

Education

There is a need for a campaign about the safety of medicines in the elderly. (8)

There is a need for an information campaign on the pharmacovigilance system and ADR reporting / need to engage healthcare professionals. (4, 11, 12,17, 19, 20, 35, 38, 40, 41, 45)

Need to educate healthcare professionals on SPCs, "Dear Doctor Letters" etc. (35)

Methods including distribution

Streamline communication channels to users of medicines / support healthcare professionals with ways to receive urgent safety messages. (3, 16, 35)

Ensure that all relevant stakeholders should get information about the safety of medicines. (5, 9, 11, 13, 19)

Information provision should be multi-layered in terms of complexity. (13, 35, 38)

EU regulators should routinely use the WHO confidential e-mail network (Vigimed) to help developing country regulators (47)

Community pharmacist organisations have electronic alert systems which could be utilised (12)

Distributors of medicines could be more actively involved in communicating about safety concerns (especially to pharmacies) (23).

Other

We need innovative methods to communicate with healthcare professionals and patients (19, 22, 35, 38)

Whenever ADR data are presented, there interpretation should be explained (35).

One should create a stakeholder partnership on better communication (22)

Need an EU working group with healthcare professionals on risk communication (35).

Need to proactively engage the media and help them understand benefit risk (35)

Outcome and quality management / audit

Outcomes

Competent Authority influence on health outcomes is weak. (7)

We should measure the impact of the pharmacovigilance systems (34, 35, 36, 47)

Routinely assess the outcomes of regulatory actions on healthcare (3, 7, 22, 35, 36, 38, 40, 41, 47, 48)

Data on the effectiveness of regulatory action and communications need to be collected (35, 36)

Measurement of impact needs to be a learning process (35)

There should be a legal requirement to measure the impact of action taken (40, 47)

More research is needed into the impact of regulation (35, 45, 48)

Research is needed into the methodology of outcome measurement (41, 45)

Quality management / audit

There should be legal requirements to have systems to respond to signals (47)

Quality management should be applied to the pharmacovigilance system (including the competent authorities) (2, 5, 9, 16, 19, 35, 36, 41)

We need agreed standards and SOPs 'Good Pharmacovigilance Practices' (16, 19, 22, 29, 32, 35, 36, 8).

Internal audits of the competent authorities are required (20, 35, 36, 38).

EMEA quality management should be used to support that in the MS authorities (35).

Continuous education of pharmacovigilance staff in the authorities is required (35, 36).

Improved resource in PhV across the authorities is essential to ensure quality systems (35, 36).

Benchmarking and sharing of best practices at Member State level is required (18, 33, 35, 39, 41)

Herbal pharmacovigilance

Data

Need a modified ADR reporting form for herbals (15)

Need work on the applicability of data mining to herbal vigilance (15)

Need to investigate patient reporting (15, 37)

Need to investigate reporting by herbal practitioners (15)

We need greater use of observational data in herbal vigilance (need to research the methodology used) (15, 37)

Users frequently do not report use to conventional healthcare professionals (15, 37)

Under reporting is a major problem with herbal ADRs (37)

Companies with herbal / well established use products should be compelled to do post marketing studies (37)

Data on volume of sales for herbal products should be collected (37).

Worksharing on Periodic Safety Update Reporting should be considered (37)

Sales and communication

Needs consideration on how to get information to herbal product users (15, 37)

Frequently no HCP at the point of sale (15, 37)

Information at the point of sale may be poor quality (15)

Internet purchasing is a problem (15)

Other

We need a specific focus on herbal pharmacovigilance (15, 47)

There is a need for collaborative work on the classification / naming of herbal products (15, 37, 47)

Poor quality products remain a problem and source of adverse reactions (15)

Some herbs have inherent toxicity (15)

There is a need for guidelines on herbal vigilance (37)

There needs to be a specific review of herbal vigilance (37)

Companies with registered traditional herbal medicinal products should have an employee responsible for vigilance (37)

The full legal requirements for vigilance should apply to herbal products (37).

There is a need for criteria for risk benefit assessment for traditional herbal medicinal products as they have no indication (37).

Pharmacovigilance actions have lead to companies moving some herbal products to other consumer goods sectors (37).

Other comments

There should be a workshop on the variation regulation. (24)

There should be more effective regulation of internet pharmacies. (3)

Centrally authorised innovative medicines should be prioritised. (3)

The EU should provide greater support to pharmacovigilance in resource poor countries (47)

The International Conference on Harmonisation does not include relevant stakeholders and is too influential in pharmacovigilance (48)

The pharmacovigilance requirements should differentiate between types of product based on knowledge about their safety – risk based pharmacovigilance (18, 20)

Any changes to the pharmacovigilance system for human medicines should not be automatically transferred to the system for veterinary medicines (21).