EUROPEAN COMMISSION
ENTERPRISE AND INDUSTRY DIRECTORATE-GENERAL

Consumer goods
Pharmaceuticals

Brussels,
April 2008

STRATEGY TO BETTER PROTECT PUBLIC HEALTH BY STRENGTHENING AND RATIONALISING EU PHARMACOVIGILANCE:

ANALYSIS OF THE RESULTS OF THE PUBLIC CONSULTATION ON LEGISLATIVE PROPOSALS

1. INTRODUCTION

The services of the European Commission have publicly consulted stakeholders on its Strategy to Better Protect Public Health by Strengthening and Rationalising EU Pharmacovigilance. The public consultation has been in two parts:

- The first part of the consultation had the objective of collecting the views of stakeholders on the community pharmacovigilance system in general, including comments on the current functioning of the system and how it might be further developed. The first part of the consultation was conducted between 16 March 2006 and 12 May 2006 (although responses were accepted up to July 2006) with consultation documents placed on the Commission DG Enterprise and Industry Pharmaceuticals website. To facilitate the public consultation the Commission services held two workshops in April 2006 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. In addition to the workshops the consultation was presented to the scientific and policy committees of the European medicines regulatory network. The results of this first part of the consultation led to the announcement in February 2007 of the Commission Pharmacovigilance Strategy and the strategy and a detailed analysis of the consultation response can be found at: http://ec.europa.eu/enterprise/pharmaceuticals/pharmacovigilance_acs/index.htm.

- The second part of the consultation was based on draft proposals for changes to EU legislation relevant to the safety of medicines. The second part of the consultation was conducted between 5 December 2007 and 1 February 2008 with consultation documents placed on the Commission DG Enterprise and Industry Pharmaceuticals website with a link to "Your Voice in Europe". The consultation document was also e-

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mailed to those stakeholders who had submitted a response to the first part of the consultation in 2006. In addition, to facilitate the provision of consultation responses by medicines regulators, the consultation was presented in detail to the scientific and policy committees of the European medicines regulatory network. The public consultation document can be found at: http://ec.europa.eu/enterprise/pharmaceuticals/pharmacovigilance_acs/index.htm.

This document presents an analysis of the response to the second part of the consultation.

2. CONTRIBUTERS

The Commission consultation received 81 contributions.

In summary:

- 5 responses from patient and consumer groups
- 16 from healthcare professional groups and academics
- 26 from regulators including the European Medicines Agency Committees, individual European medicines agencies and regulatory authorities outside the EEA.
- 28 from industry including the relevant European Industry Associations
- 6 others, including the European Monitoring Centre for Drugs and Drug Addiction, the International Network of Safe Medication Practice Centres, the International Society of Drug Bulletins, and European and International health insurance associations.

List of those providing a written contribution to the public consultation

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

Patients and consumers (5)

1. The European Consumers' Organisation (BEUC)

2. European Patients Forum

3. European Cancer Patient Coalition (ECPC)

4. Rare Diseases Europe (EURORDIS)

5. European AIDS Treatment Group (EATG)

Healthcare professionals and academics (16)

6. Standing Committee of European Doctors (CPME)

7. European Association of Hospital Pharmacists (EAHP)

8. The Pharmaceutical Group of the European Union (PGEU)

9. EuroPharm Forum (network of national pharmaceutical associations and the WHO Regional Office for Europe)

10. The European Council for Classical Homeopathy and the European Forum for Complementary and Alternative Medicine (ECCH and EFCAM)

11. Association française des Centres régionaux de Pharmacovigilance

12. Bundesvereinigung Deutscher Apothekerverbände (Federal Union of German Associations of Pharmacists) (ABDA)

13. International Federation of Catholic Pharmacists

14. European Pharmaceutical Students Association (EPSA)

15. Maria Del Zompa and Raffaella Ardau, Section of Clinical Pharmacology, University of Cagliari, Italy

16. Céline Villier, Pharmacist, Centre Régional de Pharmacovigilance de Grenoble (Grenoble Regional Pharmacovigilance Centre)

17. Mondor Hospital, Assistance Public, Hôpitaux de Paris

18. Professor Saad Shakir, Director, Drug Safety Research Unit, Southampton, UK

19. Professor Stephen Evans, Medical Statistics Unit, Department of Epidemiology and population Health, London School of Hygiene and Tropical Medicine (LSHTM)

20. Patrick Waller, Consultancy in Pharmacovigilance and Pharmacoepidemiology, UK

21. Professor DK Theo Raynor, Professor of Pharmacy Practice, University of Leeds, UK (also Executive Chairman of LUTO Research Limited - leaflet testing service)

Regulators (26)

22. Co-ordination Group for Mutual Recognition and Decentralised Procedures – human of the European Medicines Agency (EMEA CMDh)

23. Pharmacovigilance Working Party of the European Medicines Agency (EMEA PhVWP)

24. Committee for Human Medicinal Products (EMEA CHMP)

25. European Medicines Agency (EMEA)

26. Maltese Government

27. Hungarian National Institute of Pharmacy

28. Austrian Medicines Agency (Österreichische Agentur für Gesundheit und Ernährungssicherheit GmbH) (AGES)

29. Belgian Federal Agency for Medicines and Health Products (FAMHP)

30. French Government

31. German Federal Ministry of Health in consultation with the Federal Institute for Pharmaceutical and Medicinal Products and the Paul-Ehrlich Institute (Stellungnahme

des Bundesministeriums für Gesundheit abgestimmt mit dem Bundesinstitut für Arzneimittel und Medizinprodukte sowie dem Paul-Ehrlich-Institut)

32. Netherlands Medicines Evaluation Board and the Ministry of Health, Welfare and Sports (CBG/MEB)

33. Danish Medicines Agency (DKMA)

34. Agencia Italiana del Farmaco Italian National Pharmacovigilance Committee (AIFA)

35. UK Medicines and Healthcare products Regulatory Agency (MHRA)

36. Czech State Institute for Drug Control (SUKL)

37. The Office for Registration of Medicinal Products, Medical Devices and Biocidal Products of Poland

38. Infarmed I.P. (Portuguese Medicines Agency)

39. Medical Products Agency, Sweden. (MPA)

40. State Institute for Drug Control, Slovakia

41. Prof. dr. A.C. van Grootheest, Netherlands Pharmacovigilance Centre, Lareb, University of Groningen

42. Norwegian Medicines Agency

43. Patrick Salmon, Irish Medicines Board

44. Non-EEA Regulatory Agency (response will not be made public)1

45 Health Canada

46. Non-EEA Regulatory Agency (response will not be made public) 2

47. Spanish Government

Industry (28)

48. European Federation of Pharmaceutical Industries Associations (EFPIA)

49. Association of the European Self-Medication Industry (AESGP)

50. The European Generic medicines Association (EGA)

51. European Biopharmaceutical Enterprises (EBE)

52. EuropaBio

53, European Vaccine Manufacturers (EVM)

54. European Association of Pharmaceutical Full-Line Wholesalers (GIRP)

55. European Coalition on Homeopathic and Anthroposophic Medicinal Products (ECHAMP)

56. The Association of the British Pharmaceutical Industry (ABPI)

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

58. Pharmaceutical Research and Manufacturers of America (PhRMA)

59. CSL Behring GmbH

60. Galpharm

61. GE Healthcare

62. Gurdyal Kalsi, MDS pharma services

63. Johnson and Johnson

64. Merck

65. Norvartis

66. Organon (Schering-Plough Corporation)

67. Pfizer

68. Pharmiceutics LLC

69. PhytoLab GmbH & Co. KG

70. Reckitt Benckiser Healthcare

71. Combino Pharm

72. Wyeth Pharmaceuticals

73. Zentiva

74. Dr Wolfgang Matthies, Medical Consulting and Qualified Person of Pharmacovigilance for Ecolab Europe

75. Verband der Arzneimittelimporteure (VAD)

76. numbered in error: no response numbered 76

Others (6)

77. Health Action International Europe (HAI Europe) + Medicines in Europe Forum + International Society of Drug Bulletins (ISDB)

78. European Monitoring Centre for Drugs and Drug Addiction (EMCDDA)

79. Association Internationale de la Mutualite (AIM)

80. European Social Health Insurance Forum (Medicine Evaluation Committee)

81. European Pharmaceutical Law Group

82. International Network of Safe Medication Practice Centres (INSMPC)

3. OVERVIEW OF COMMENTS RECEIVED

In this section a high level summary of the key messages of the consultation response is provided. Annex 1 provides a more detailed breakdown of the comments received from the contributors to the consultation. In addition the individual responses are placed on the web at the following web address:

http://ec.europa.eu/enterprise/pharmaceuticals/pharmacovigilance_acs/index.htm.

1. General Feedback

There was very strong support for the objectives pursued and for the draft proposals overall with only two of eighty-two responses not welcoming the proposals. There was strong support for improving the robustness of EU pharmacovigilance with clear legal provisions and better use of resources i.e. resources used to monitor the safety of medicines and take action to reduce risks to users rather than used to meet duplicative administrative requirements.

2. Legislative Strategy

Relatively few stakeholders commented on the legislative strategy as such[1]. Those that did were supportive although some industry responses commented that use of a directive could lead to disharmony through Member State transposition / implementation.

3. Rationalise EU decision-making

There was unanimous support for the need to rationalise EU decision-making on safety issues. This support included strong endorsement for the establishment of an automatic pharmacovigilance referral procedure with non-discretional referral triggers placed on the Member States. Questions were raised and suggestions made regarding the scope of products covered by the procedures (notably whether centrally authorised products were included) while the scope of the triggers was generally supported (with reservations from a minority of industry responses about inspection findings being a trigger).

The proposed operation of the referral procedures was generally supported, however, numerous comments were made on the detail. The more consensual of the latter were that companies should be notified of referrals affecting their products, be consulted more explicitly and have an appeal procedure, that divergences in the views of the committees would need careful handling, and that the existing Coordination Group for Mutual Recognition and Decentralised procedures – Human (CMD-H) could have a role in

[1] The legislative strategy proposed is a directive of the European Parliament and the Council amending Directive 2001/83/EC and, a regulation of the European Parliament and the Council amending Regulation (EC) No 726/2004

implementation of decisions. There was unanimous support for the outcome of the referrals being legally binding. The proposal to hold public hearings for all but the most urgent referrals received a mixed response. While consumers and doctors strongly welcomed the proposal for hearings, regulators and industry expressed some concern that public hearings would be resource intensive and should not be systematic (there was, however, a reasonable level of support for ad-hoc public hearings).

The proposal to create a new Pharmacovigilance Committee with a clear legal identity and defined remit was almost unanimously supported. However, many stakeholders called for greater clarity on the precise remit of the new committee, its role on centrally authorised products (which was not specified in the consultation document) and its interface with the existing committees notably the Committee on Human Medicinal Products (CHMP) and CMD-H. There was a very wide spectrum of suggestions on remit, from the new Pharmacovigilance Committee having complete autonomy from the existing EMEA Committees for post-authorisation issues and total authority in decision-making, to stakeholders wishing the CHMP to have complete authority over benefit risk assessment with emphasis put on the importance of the knowledge and expertise brought by the authorisation rapporteur team and from the integration of pre and post-authorisation assessment. The important role of the CMD-H was stressed particularly with respect to nationally authorised products and a role for CMD-H in decision-making and implementation of decisions was suggested. Regarding the composition of the new Pharmacovigilance Committee there was support for patient and healthcare professional representation, as well as, support for maximising the pharmacovigilance expertise available. Linked to the latter point, some stakeholders called for pharmacovigilance experts to be selected rather than being appointed by Member States.

4. Rationalise roles and responsibilities / establish clear standards

There was unanimous support for clarifying and rationalising the roles and responsibilities of those stakeholders having requirements provided for in the pharmacovigilance legislation. Some stakeholders suggested providing explicit tasks for healthcare professionals and patients in the legislation and two responders suggested that the role of industry in pharmacovigilance was too great.

The proposal for strengthening the obligation on industry to inform about changes to the benefit risk balance of its products including when this results from clinical trial results was generally welcomed with regulators suggesting the provision on clinical trial reporting be even more explicit and industry suggesting a need for greater clarity and for the requirements to be delineated. There was similarly support for the new obligation on industry to keep its product information up to date with regulators suggesting that labelling recommendations on the EMEA website should be more binding and industry requesting greater clarity of the scope of the requirement.

There was strong support for the principles of outcome and process audit although greater clarity was requested on the processes for these functions. Similarly, inclusion of requirements for monitoring safety data and signal detection were welcomed although more precise provisions and delineations of responsibility were suggested (notably with a key role for the new Pharmacovigilance Committee suggested).

Among the small number of stakeholders who commented, there was support for the proposal that Member States may delegate certain pharmacovigilance tasks to each other although there was a request for details on the scope of such tasks.

There was unanimous support for the introduction of Good Vigilance Practices (GVP) with suggestions for broad stakeholder involvement in its (early) development and respect for existing international harmonisation with diverse comments on the proposed scope and the interface with existing EU guidance (i.e. Volume 9A of Eudralex).

The proposal for an overarching provision obliging the Member States to enforce penalties for non-compliance with pharmacovigilance provisions were broadly welcomed with industry requesting a clear definition of the Member State measures, procedures and an appeal mechanism.

5. Company pharmacovigilance system and inspection provisions

There was strong support for rationalising the way the authorities oversee the company's pharmacovigilance system. The proposals will allow companies to make changes to their systems in a timely manner while also maintaining oversight by the authorities. Five of eighty-two stakeholders interpreted the proposal to submit a summary of the pharmacovigilance system at authorisation and maintain a detailed dossier on site in the form of a 'Pharmacovigilance System Master File - PSMF' as reducing regulatory scrutiny[2]. Industry voiced strong concerns about internal audit reports being included in the PSMF.

Amongst the relatively few comments on the proposals to increase EU coordination of pharmacovigilance inspections was the suggestion for the EMEA to maintain a database of reports, the suggestion for a risk based system to be introduced, and the suggestion for minimum EU inspection standards to be developed. The industry requested clarity regarding the process for audit reports and company comments on them, and on the interface with GMP inspections. Guidance was requested on the concept of 'serious deficiencies'.

Regarding the proposal to create a specific supervisory authority for centrally authorised products for the purposes of pharmacovigilance inspections, the industry suggested that the site of the main pharmacovigilance function rather than the country of residence of the Qualifies Person should dictate the authority and there were various questions raised on the scope of responsibilities of the authority.

6. Rationalise and strengthen risk management planning

There was very strong support for rationalisation and strengthening of the role of risk management planning in pharmacovigilance thereby making safety monitoring and risk minimisation driven by the knowledge of the safety of a product, more proactive and based on more robust data. There was a request for the terms risk management system and risk management plan to be merged and for the follow up and maintenance of risk management plans to be clarified. There was a call for clarity on which products would need a risk management plan submitted at authorisation application but unanimous agreement that the key measures in the plan be made legally binding by their inclusion as conditions of the marketing authorisation (although it was suggested that key elements / a

[2] This may have been because the consultation paper insufficiently emphasised that the current very bureaucratic system obstructs companies from having a modern, flexible system and that the new proposals include wide ranging powers for the authorities to request submission of the PSMF and to send inspectors to the companies who would have to provide access to their premises and the PSMF.

summary of the risk management plan be annexed to the marketing authorisation rather than the entire plan). Industry requested one EU risk management plan without the need for Member State negotiations and amendments.

There was broad support for the introduction of 'intensive monitoring' and an 'intensive monitoring list' for new products with studies, additional safety monitoring or restriction on use as risk management conditions in the marketing authorisation. There were requests for clarification on whether the provisions were aimed at all new substances, could be applied whatever the authorisation route and on the inclusion criteria, maintenance process and removal mechanism of the intensive monitoring list. Additional comments included the need to explain the purpose of the list to stakeholders and the need to include already authorised products on the list. A role for the Pharmacovigilance Committee in overseeing the list was suggested.

There was strong objection to the proposal to replace the current 'exceptional circumstances marketing authorisation' with the 'intensively monitored' products. The objections fell in to two groups: 1. those that considered that 'exceptional circumstances marketing authorisations' were useful for non pharmacovigilance related issues, and, 2. those that understood the proposal to be a lowering of the standard for placing a product on the market[3].

The consultation paper also proposed to amend the criteria for taking regulatory action post authorisation (amendments to Articles 116 and 117 of Directive 2001/83/EC) simplifying the criteria basing them on the benefit risk balance (deleting the sub clause of efficacy) and deleting the concept of normal conditions of use as this is not defined and could be interpreted as restricting regulatory action in the case of a major public health issue related to off-label use (e.g. in children). The proposals then brought the authorisation criteria in line to have a rational symmetry of criteria for putting a product on and taking it off the market. While some industry responses question the deletion of normal conditions of use, major objections were received regarding deletion of the efficacy sub-clause. Some stakeholders understood this to mean that products without efficacy could be put on the market i.e. a lowering of the requirements for authorising a medicine. It appears that the rational for the proposed changes and particularly the concept of efficacy being a sub clause of benefit risk (a positive benefit risk being impossible with no efficacy) was not well explained in the consultation paper.

7. Legal basis for requesting PASS

There was unanimous support for a clear legal basis for the authorities to request post authorisation safety studies (PASS). There was also support for the proposed procedure and for the inclusion of the final requirement as a condition of the marketing authorisation thereby making it legally binding.

The consultation paper proposed an inclusive definition of post-authorisation safety study which thereby defined the scope of studies which could be requested in the event

[3] The intention was, in reality, to increase the robustness of post-authorisation follow up of the majority of new innovative products by applying to them the annual reassessment process currently used for 'exceptional circumstances marketing authorisation' products.

of serious safety concerns. There were diverse comments on the definition, many positive and supportive, however, some industry responses suggested a narrower definition[4].

8. Post-authorisation safety studies (PASS) - principles and oversight

There was strong support for guiding principles and oversight of a subset of PASS, that subset being non-interventional PASS, initiated, managed, or financed by the marketing authorisation holder and that involve collection of data from healthcare professionals or patients. Some industry responses questioned the precise limits of the scope of the oversight including whether non-EU studies are included[5], while some responses from both industry and regulators called for the interface with risk management plans to be clarified. The guiding principles were supported while having a scientific objective was also suggested as such a principle. The key comments on the procedure were for protocol suggestions from the regulators to be binding and support for making public recommendations for product labelling based on the study results. Some stakeholders suggested that such recommendations should be legally binding.

9. Rationalise single case adverse drug reaction reporting

The proposals to strengthen and rationalise expedited single case adverse drug reaction reporting received very strong support including strong support for simplification of the rules based on electronic reporting with full utilisation of modern information technology. The important role of Member States, and for some countries, of regional centres in stimulating reporting and improving the quality of reports was emphasised. Numerous stakeholders from across the different groups suggested that the causality criteria that had been proposed needed amending or that the concept of suspected adverse reaction should be maintained.

There was strong support for the use of Eudravigilance as a common tool to support pharmacovigilance and stakeholders stressed the importance of national regulators and companies (i.e. those with legal responsibilities for safety monitoring) having full access to the data on Eudravigilance (for transparency see Section 11). A small number of stakeholders expressed concern about the technical capabilities of the Eudravigilance 2007 version and emphasised that further development would be necessary to support the proposed new pharmacovigilance rules.

There was unanimous support for marketing authorisation holders electronically reporting all serious non-EU adverse reaction cases to Eudravigilance only. In contrast the proposal that all EU domestic reports be electronically reported to Eudravigilance and thereby be made available to the Member States received mixed feedback: while five of twenty-six regulator responses suggested that reports should be send to Eudravigilance and the country of origin of the report, the industry supported reporting only to Eudravigilance but suggested that non-serious reports should be electronically reported periodically rather than on an expedited basis.

[4] this may be explained by a misunderstanding of the purpose of the definition, considering it to define the scope of regulatory oversight of studies (rather than defining the scope for requesting them).

[5] they explicitly were not included in the scope

There was strong support for the principle of providing a clear legal basis for patient reporting although numerous suggestions were received on how this should be best achieved. The important role of healthcare professionals in interpreting symptoms and signs was stressed as was the relationship between patient and professional. Overall there was support for making a variety of methods available to patients to report there suspected adverse reactions. There was support for information on adverse reaction reporting to be included in patient information leaflets of intensively monitored products while the inclusion of forms in packaging was not encouraged. It was suggested to introduce a symbol onto the packaging of intensively monitored products rather than having a warning on the packaging. The draft proposals suggested that paper reports be sent by patients to the marketing authorisation holders in order to distribute the work of the data entry necessary for electronic reporting and data management. However, there was a strong call, including from the regulators, for patient reports to be sent directly to the national competent authority for medicines.

The proposal that the EMEA make available within five-years a web-based structured reporting facility to Eudravigilance was strongly welcomed by patient and healthcare professional groups. In contrast some regulators saw this as bypassing the national medicines authority and being detrimental to data quality.

With the exception of the European Medicines Agency (EMEA) itself, there was unanimous support for the EMEA having a core but delineated role in literature monitoring and reporting to Eudravigilance of adverse reaction case reports. The high work load involved in literature monitoring was stressed as was the fact that because of reporting requirements to non-EU regulators, EMEA processes would have to be transparent, meet strict criteria and the data in Eudravigilance would have to available to the marketing authorisation holders for them to then be spared having to duplicate the work. Furthermore, the industry suggested that the resource saving for new innovative drugs would not be major as marketing authorisation holders would wish to carefully monitor the literature independently of any legal reporting requirements. Linked to this point was a suggestion that the EMEA role be limited to old established products (i.e. be based on active substances where there was no patent or regulatory data protection). It was emphasised that there would need to be clarity as to whether the marketing authorisation holders still had to monitor local market literature and non-EU regulators and the industry pointed out that this would be an opportunity for international collaboration including on monitoring standards.

There was strong support for clarifying the place of medication error reporting within regulatory pharmacovigilance. Comments called for greater clarity of the provisions particularly the respective roles and responsibilities of the different parties, however, amongst those expressing a view there was support for placing an obligation on Member States to ensure exchange of data between the competent authority for medicines and any national authority responsible for patient safety. The need for data to be submitted to Eudravigilance, the need for such reports to be earmarked in the database (for data analysis) and the need to address anonymous reporting were highlighted. It was suggested that "near misses" and not just medication errors resulting in an adverse reaction should be reported within the regulatory pharmacovigilance system.

Amendments and deletions to certain definitions related to adverse reactions were suggested in the consultation paper. The simplification of the definition of adverse reaction was proposed to support medication error reporting and certain other definitions were proposed for deletion as they were considered redundant as far as the legal

provisions were concerned. These proposals stimulated numerous comments including the need to respect internationally agreed definitions, as well as, an array of suggestions for new definitions. Although the proposed amendment of the definition of "adverse reaction" received both negative as positive comments, no clear rationale was provided against the proposed change.

To improve the pharmacovigilance of biological products including biosimilars the consultation paper proposed that Member States ensure that biological medicinal products that are the subject of adverse reaction reports be identifiable. This proposal resulted in numerous comments mainly from the industry. While some responses suggested that delegating this responsibility to the Member States could result in disharmony (and proposals for the Pharmacovigilance Committee to issue guidance were put forward) the innovative industry sector suggested that the EU legislation be used to force distinct names (distinct INNs) for biosimilar medicinal products and to outlaw biosimilar substitution at the level of the pharmacy.

10. Rationalise periodic safety update reports (PSURs)

There was strong support for rationalisation of periodic safety update reports (PSURs). There was support for linking PSURs to risk management planning but a call for this link to be more explicit. The reorientation of PSURs to be risk benefit evaluations including assessment of all relevant data rather than including data line-listings was supported although concerns were expressed about the impact on internationally agreed formats.

There was full support for PSURs to be submitted electronically with strong industry support for exclusive submission to the Pharmacovigilance Committee and thereby distribution to the rapporteurs and Member States, while three Member State authorities suggested that the authorising authority should also be send a report directly by the Marketing Authorisation Holder. The need to define, test and implement a standard for electronic PSURs was emphasised.

For old established products the intention in the consultation paper was that routine, uncoordinated PSURs for old established products should not be a default requirement of the legislation but rather that the Pharmacovigilance Committee would build on the existing work-sharing project being conducted by the Heads of Agencies and Pharmacovigilance Working Party. Specifically, based on a judgement of the Pharmacovigilance Committee of the risk posed, including the need for product information to be updated, PSURs covering a specified period of time would be required to be submitted by a deadline for all products containing a particular active substance. The comments received were diverse with many interpreting that no PSURs would ever be submitted for older products[6]. The comments received are, however, supportive of some PSUR reporting for older products based on risk and for this to be rationalised.

In terms of the procedure for PSUR assessment, overall there was strong support for a key role for the Pharmacovigilance Committee including making public its recommendations for product labelling. Medicines regulators called for the recommendations to be more binding over the companies.

[6] It appears that the proposals to rationalise reporting for old established products were not sufficiently explained in the consultation paper.

11. Strengthen transparency and communication

There was unanimous support for the need to strengthen transparency and communication in pharmacovigilance. Many stakeholders emphasised that risk information should not be presented in isolation but be balanced with information on the benefits of medicines and the importance of respecting both commercial and personal data confidentiality was stressed. The need for stakeholder engagement and consultation was also emphasised by different stakeholder groups.

The proposals for both EU and National medicines safety web-portals were strongly supported although clarity regarding the interface with existing websites such as the Commission Public Health Portal and EMEA EudraPharm was requested. The spectrum of information to be made public was broadly supported although the diverse and divergent comments can be summarised as, at one extreme requesting that only summaries of final documents and conclusions be added to the website and, at the other that a much greater level of transparency be implemented including all correspondence and interim assessments.

The proposals on increased transparency of adverse reaction data on Eudravigilance were welcome except by some industry responses. The need to make public aggregated adverse reaction data which is clearly presented and explained for stakeholders in an EU-agreed format was emphasised. Proposals for details of individual reports to be released on request were welcomed by many stakeholders but concerns were expressed about personal confidentiality not being respected and regarding the workload involved.

There was strong support for enhanced EU coordination of important safety messages including the timing of their distribution. The industry requested that the proposals go further in committing the Member States to single EU safety communications while the Member States stressed the importance of local factors and cultural elements.

The proposals on the provision of medicinal product information to support the development of EudraPharm and the EU pharmacovigilance medicinal products dictionary raised comments regarding the scope of the work and the interface with ongoing projects. Notably, clarity was requested as to whether the intent was to feed data to EudraPharm or the EU pharmacovigilance medicinal products dictionary or both and the need for respect of the ongoing ICH and ISO projects was emphasised. It was suggested to limit the scope to authorised medicinal products and to prolong the deadlines on industry.

12. Strengthen product information

Stakeholders were strongly supportive of the need to improve EU product information including the penetration of key information including safety information. Stakeholders emphasised that safety information should be presented in the context of benefit and that a synthesis of key information was need rather than a presentation of only key safety information. There were suggestions for a key information or summary section to be added to the beginning of product information and a strong call for measures based on key information to be supported by detailed guidelines developed based on wide consultation and careful testing. The industry requested a long implementation phase to minimise the cost implications of the proposed changes.

13. Other major comments not falling into sections 1 to 12

The comments received are divers and readers may wish to see Section 13 of Annex 1 to read the individual comments for themselves.

Unit F2,
DG Enterprise and Industry,
European Commission,
April 2008.

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:

The numbers recorded in the analyses in the thirteen sections correspond to the stakeholder contribution as listed in Section 2 of the main paper. The individual responses will be placed on the web at the following web address: http://ec.europa.eu/enterprise/pharmaceuticals/pharmacovigilance_acs/index.htm.

Detailed drafting suggestions received from stakeholders are not recorded in this annex.

1. Overall Feedback on the proposals:

- Proposals welcomed/ general support/ good for public health: 1, 2, 3, 4, 5, 6, 8, 10, 12, 14, 18, 19, 20, 22, 23, 24, 25, 26, 27, 29, 31, 32, 33, 35, 37, 38, 42, 45, 47, 48, 49, 50, 51, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 67, 70,
- Proposals not welcomed: 7, 77

2. Legislative Strategy overall

Supportive: 1, 2, 3, 5, 6, 14, 18, 20, 22, 27, 32, 33, 42, 60

Not supportive

- Concern that using a directive may result in continued Member State disharmony / explicit call for use of a regulation for Chapter IX of Directive 2001/83 49, 55, 58, 65
- Call for single piece of legislation / single regulation needed 58
- Support for a risk based, proportionate approach 60
- Ensure proportionality and subsidiary are respected 57, 58
- Commission should not have the authority to change the pharmacovigilance title through comitology (i.e. without going to the Council and Parliament) 77
- improved implementation of the current framework without changes to legislation 80
- We must not have more deregulation 77

2.1 Support / need for better regulation / rationalisation

Supportive: 3, 4, 14, 20, 22, 23, 29, 33, 35, 38, 45, 47, 48, 49, 50, 51, 53, 55, 56, 57, 58, 63, 65, 67, 70

- Include the legal basis for more work sharing 22, 23, 29, 33, 35
- Have a lead member state for issues related to purely nationally authorised products 48, 51, 53, 56, 57
- A careful impact assessment is required 25
- Need better public consultation on guidelines under development 77

2.2 Overall simplification

Supportive: 3, 4, 6, 7, 20, 23, 29, 33, 35, 38, 45, 48, 49, 51, 53, 56, 57, 58, 60, 62, 63, 65, 67, 70

Not supportive: 77

- Simplification / cost savings should not be at the expense of public health protection 7, 8, 11, 14

2.3 Industry funding of pharmacovigilance to be allowed

Supportive 16, 25

Not supportive 77, 79, 80

- Public funding must be adequate 77, 79, 80
- Need greater clarity on funding of pharmacovigilance 35
- Pharmacovigilance should be funded publicly / independent from the industry 34, 77, 79, 80
- The scope of what activities could be funded by industry needs to be specified (e.g. academic post-authorisation safety studies) 20
- Committee should be independently funded / how will the work of the committee be funded / Committee should be adequately funded 3, 4, 5, 35
- Support for funding rapporteurs on the committee on pharmacovigilance 39
- Committees work should not entail new fees / care that committee does not inflate fees 49, 57

- Fees should be proportionate 49, 55

3. Rationalise EU decision-making on safety issues, overall
Supportive: 1, 2, 3, 4, 5, 6, 7, 11, 20, 22, 23, 25, 26, 28, 29, 31, 32, 35, 42, 47, 48, 49, 50, 51, 53, 55, 56, 57, 58, 60, 61, 63, 65, 67, 71

3.1 Article 31 and 36 of Directive 2001/83/EC – maintained as legal tools but not used if the criteria for automatic pharmacovigilance referral are met.
Supportive 22, 23, 29, 30
- Greater clarity is required / is the reference to paragraphs 1 *and* 2 of Article 101k 30, 31

3.2 Create automatic pharmacovigilance referral (Article 101k) based on the existing Article 107 of Directive 2001/83/EC
Supportive: 1, 2, 3, 6, 8, 12, 20, 22, 23, 25, 29, 35, 39, 42, 47, 48, 49, 50, 51, 53, 56, 57, 58, 63, 65, 71
- Clarify the scope of products (medicine authorised in just one Member State / centrally authorised products)/ products authorised in just one MS should not be caught 33, 35, 48, 51, 53, 56, 57, 58, 65
- Clarify that referrals may be restricted to certain indications / certain routes of administration 32
- Clarify /increase the consultation of the Marketing Authorisation Holders 39, 48, 49, 51, 53, 56, 57, 58, 63, 65
- Clarify the interface with urgent safety restrictions / allow an urgent safety restriction at the start of the procedure 20, 22, 23, 29
- After the referral nationally authorised products should not be transferred to the mutual recognition procedure 22, 35

3.3 Clear criteria for non-discretional notification / referral relating to medicinal substances or groups identified by substances they contain (Article 101k)
Supportive: 6, 7, 8, 11, 12, 16, 20, 39, 42, 48, 50, 51, 53, 56, 57, 58, 71
- Companies should not withdraw a product without warning: 7, 8, 9, 12
- Member States should not be able to suspend ahead of the EU decision 48, 51, 53, 56, 57
- Companies should be notified at the same time as the authorities / should get all the scientific information available from the referring Member State at the same time 48, 50, 51, 53, 56, 57, 58
- Ensure the other Member States / committee on pharmacovigilance are notified 30
- Include criteria of when a positive risk benefit balance is in question 20
- Clearly define that safety is the trigger 39, 47
- Clearly define those issues that would not go through this referral and which committee would be responsible for them / greater clarity required 22, 35
- Inspection deficiencies should not be a trigger /concern re inspection result trigger 48, 51, 53, 56, 57, 58, 63, 67
- Include new warnings in the scope 42
- Harmonisation recommendations and oversight of implementation should be done by CMDh (Coordination Group for Mutual Recognition and Decentralised procedures – Human) 22

3.4 Make clear, light procedures and ensure companies follow the EU decisions.
Supportive: 1, 6, 8, 12, 39, 48, 49 50, 51, 53, 56, 57

- There is a need for / clarify the company appeal procedure 39, 48, 49, 51, 53, 56, 57, 67
- Greater clarity on the light procedures needed 48, 51, 53, 56, 57, 63, 64, 65, 67

3.5 Committee on Pharmacovigilance assesses the issue and makes a recommendation to the EMEA Committee for Human Medicinal Products (CHMP) which, in turn, adopts an opinion within 90-days of the notification
Supportive: 1, 3, 6, 7, 10, 11, 16, 19,
Not supportive 24, 25, 79, 80

- How would divergent opinions between the Pharmacovigilance and CHMP be resolved / need clarity as to whether CHMP would have to follow the recommendation 24, 30, 37, 39
- CHMP opinions should include consideration of alternative treatments and whether they could create a new public health concern 25
- Selection of rapporteurs is not clear 39

3.6 Binding Commission Decision / binding decision
Supportive: 1, 2, 5, 6, 22, 39, 48, 49, 50, 51, 53, 56, 57, 71

- Clarify the temporary measure that are possible 48, 51, 53, 56, 57
- Communicate if no further action is required 48, 51, 53, 56, 57, 65
- Specify the time limit on Member States to comply 39

3.7 Formalise a committee at the EMEA of pharmacovigilance experts. [Reg 726/2004 Article 61], overall,
Supportive: 1, 2, 3, 4, 5, 6, 7, 8, 10, 11, 12, 14, 16, 19, 20, 22, 23, 26, 28, 29, 30, 31, 32, 35, 36, 42, 47, 48, 49, 50, 51, 53, 55, 56, 57, 58, 63, 64, 65, 71, 79, 80
Not supportive 24, 27

- Need greater clarity on the interface with CHMP / clearer mandate / the role in decision-making on different types of marketing authorisations and procedures needs to be clarified 22, 23, 25, 26, 29, 30, 31, 32, 33, 35, 36, 39, 42, 47, 48, 51, 53, 56, 57, 58, 63, 64, 65, 67
- Avoid overlap of responsibilities 32, 47
- There should be separation of responsibility for pharmacovigilance decision-making from the CHMP 10, 11, 16, 19, 20, 77, 79, 80
- Pharmacovigilance Committee should have authority / make independent of CHMP 34, 35, 36, 42, 77, 79, 80
- Pharmacovigilance Committee opinions should be legally binding / make Pharmacovigilance Committee opinions on safety issues legally binding over companies and therefore fully implemented 22, 23, 29, 34, 42, 49, 77, 79, 80
- Pharmacovigilance opinions should be binding for MR/ Decentralised products 35, 42
- Pharmacovigilance Committee should have 'persuasive opinion' over national products 35
- Define the link with CMDh and for what issues that link should be used 22, 25, 30, 35
- CMDh should be able to put questions to the new committee including questions on the authorisation of medicines 22
- Pharmacovigilance Committee and CMDh to coordinate the implementation of more minor safety labelling changes 22, 35

- Create a new scientific expert committee the “Medicines Safety Advisory Board” to advise CHMP. No Member State representation. Administrative aspects of pharmacovigilance become the responsibility of the CMDh. 25
- Disagreement at the Pharmacovigilance Committee should trigger referral to CHMP 35
- The Pharmacovigilance Committee should have the power to request risk management plans / studies 77, 79, 80
- Have one committee responsible for pharmacovigilance regardless of authorisation route 33
- Benefit as well as risk needs to be considered in decision-making 30, 39, 47, 49
- The Committee on Advanced Therapies should be consulted on benefit risk issues of relevant products 26
- The Pharmacovigilance Committee should cover benefit as well as risk 23, 29, 34
- CHMP should maintain the lead for the benefit and risk of centrally authorised products pre and post authorisation 24, 25, 32, 39, 48, 51, 53, 56, 57
- CHMP should lead on benefit risk ratio / the CHMP should consider benefits and risks of medicines 25, 30, 32, 39
- CHMP should be the final committee for all decisions on granting Marketing Authorisations, variations, suspensions, and revocations 39, 48, 51, 53, 56, 57
- New pharmacovigilance committee should cover non-centrally authorised products only 24
- Having one rapporteur / reference member state through the product lifecycle leads to robust decision-making 24, 32, 39
- Use the concept of a problem owner / lead member state for nationally authorised products 32
- Concern regarding the workload of the new committee / what means will be put at the committees disposal 24, 30, 39, 49
- New committee would increase the complexity of coordination for the EMEA 25
- There is a need for an overall review of the EMEA committees for human medicines and how they interact 25, 39
- Role for signal detection and analysis should be clarified 22, 23, 25, 29,
- Industry should be routinely consulted on committee opinions 48, 49, 51, 53, 56, 57, 58, 65
- Committee should liaise with stakeholder groups /patient groups and this should be defined. 4, 5, 22
- Create a formal link to the EMEA working party on patients and consumers. 2
- Create a formal link to the Commission DG Sanco Patient Safety Working Group of the High Level Group on Health Services and Medical Care 2
- Committee to have a scientific as well as coordination role 23, 29,
- The new committees work should be based on evidence-based science and transparent procedures 48, 51, 53, 56, 57, 58, 67

3.7.1Member State Experts /expertise

Not supportive 25, 65

- The Pharmacovigilance Committee should have more independent clinical / academic experts/ co-opted members19
- The Pharmacovigilance Committee needs communication expertise 23, 29,
- The Pharmacovigilance Committee needs expertise on OTC/ homeopathic/ anthroposophic medicines 49, 55

3.7.2 Patient and Healthcare Professional representatives

Supportive: 1, 3, 4, 5, 11, 16, 25, 65, 81

Not supportive 36

- Pharmacovigilance Committee should include Member State Pharmacovigilance Committee Chairpersons 11, 16
- Need to clarify the appointment process and the role of these members 23, 29,

3.7.3 Remuneration of rapporteurs [Reg 726/2004 Article 62]
Supportive 3
Not supportive 34

- Funding for patient representatives needed 3, 4, 5

4. Rationalise roles and responsibilities and establish clear standards, overall
Supportive. 1, 2, 4, 5, 6, 11, 14, 16, 23, 25, 29, 35, 37, 44, 48, 49, 50, 51, 53, 55, 56, 57, 63, 65, 79

- Include the role of other stakeholders (consumers, carers, families, parents, social health insurance organisations) 79
- The role of healthcare professionals should be included / considered for inclusion. 7, 8, 12, 30
- Pharmacists have a critical role to play 7, 8, 12
- Too great a role / too much influence of industry 77, 79

4.1 Clear obligation on industry to inform of changes to benefit risk including results of clinical trials [Dir 2001/83Article 23]
Supportive 19, 20, 23, 25, 29, 30, 37

- Reporting clinical trial results should be an clear obligation 19, 20, 30
- Reporting should cover all studies of which the Marketing Authorisation Holder is aware 20, 30
- Reporting positive and negative study results is important 30
- Include obligation for clinical trials in third countries 25
- Obligation for clinical trials should only be company sponsored trials 48, 51, 53, 56, 57, 58, 67
- Reporting obligations should include off-label use 20
- Include obligation for products being considered for MA 25
- Add a timeframe for notification 58
- This obligation needs to be more specific / better defined/ include aspects in the Pharmacovigilance System Summary 37
- Companies will be judge and defendant 77

4.2 Clear obligation on industry to keep product information up to date including recommendations placed on the EMEA website [Dir 2001/83Article 23]
Supportive 23, 29, 39

- Need to clarify the breadth of this requirement 48, 51, 53, 56, 57
- Need to have processes to ensure consistency between product information and the web portal / clarify the follow up by Member States 39, 48, 49, 51, 53, 56, 57, 65
- Include a deadline 39

4.3 List of obligations placed on the Agency, Member States, and Marketing authorisation holders [Dir 2001/83 Article 101l], overall
Supportive: 1, 2, 3, 6, 7, 14, 23, 29, 39, 48, 51, 53, 56, 57, 79

- Role of the qualified person for pharmacovigilance is very important / list the obligations of the qualified person for pharmacovigilance 14, 23, 29,

- The qualified person should be able to delegate tasks as long as they retain oversight and review the safety profiles of all products 48, 51, 53, 56, 57, 58, 63, 64, 65
- The qualified person should not be responsible for the risk management system 58
- There is a need for a contact person for information to stakeholders in each Member State 23, 29,
- Need legal basis for marketing authorisation holders to have Member State qualified persons for pharmacovigilance 11, 16, 23, 29, 48, 51, 53, 56, 57
- Create clear obligation for the Marketing Authorisation Holder to collect data on the effectiveness of risk management planning 25
- Create an obligation for the Marketing Authorisation Holder to provide sales and utilization data 25
- Create the legal basis for the long term monitoring of patients by the marketing authorisation holder 25
- Include a description of the objectives of a pharmacovigilance system in the article that requires Member States to operate a pharmacovigilance system 25
- Including the obligation in the current Article 103 (c) and (d) regarding the MAH providing information 25
- Clarify the role of a Member State supervisory authority 30, 38, 48, 51, 53, 56, 57, 65, 67
- Avoid that list of tasks / roles on Member States is used as a hook for disharmony 67
- Keep flexibility / keep high level 39

4.3.1. Clear responsibilities for measuring the outcome of pharmacovigilance / risk minimisation actions

Supportive 2, 3, 25, 39, 47

- There is a need for standard methodologies to be developed 48, 51, 53, 56, 57, 58
- This provision needs to be clarified / interface between EMEA and Member States needs clarification / Member States critically involved in healthcare delivery for all medicines 30, 39, 47

4.3.2 Clear responsibilities for process audit

Supportive 2, 3, 39, 48, 50, 51, 53, 56, 57, 63

4.3.3 Clear responsibilities for monitoring data for new safety issues / signal detection

Supportive 35, 39, 50, 58, 63, 67, 80

- Need greater clarity on identification, evaluation and reporting of signals (including monitoring Eudravigilance data) and the role of marketing authorisation holders, rapporteurs, reference member states and the new committee 23, 24, 25, 29, 32, 35, 39, 48, 51, 53, 56, 57, 58, 63, 65, 67
- This should be a clear role for the new Pharmacovigilance Committee 30, 32, 35, 47
- Rapporteur to remain the lead for signal detection 24, 48, 51, 53, 56, 57,
- Reference Member State to remain the lead for signal detection 48, 51, 53, 56, 57
- Include signal work sharing between the Member States 23, 29, 32
- Companies will be acting as judge and defendant if they are responsible for monitoring 77

4.4 A Member State may delegate certain pharmacovigilance tasks to another Member State and the Agency makes this information public

Supportive 23, 29, 49

- The list of transferred tasks should explain that the basis is work sharing 23, 29,
- Clarify whether this transfer could extend to imposing penalties 48, 51, 53, 56, 57, 58, 67
- Marketing authorisation holders should be informed 49

- Clarify if all tasks can be delegated to the EMEA 30

4.5 Audit of the authorities: Member States report results of their pharmacovigilance processes and the Commission makes public a yearly report + EMEA audit goes to its Management Board
Supportive: 1, 3, 30, 39
- Support for pharmacovigilance audit 23, 29, 30, 39
- Audit of Member States should be through the Heads of Medicines Agencies 'BEMA' project 23, 29,
- Audit of the EMEA pharmacovigilance tasks is supported 23, 29,
- Proposed frequency for Member State audits and Commission report is too great 30, 39
- Greater clarity required 39

4.6 Standards may be published by the Commission as 'Good Vigilance Practices' [Dir 2001/83 Article 101b]
Supportive: 1, 2, 3, 5, 6, 11, 16, 20, 23, 25, 29, 35, 37, 45, 49, 50, 55, 58, 60, 61, 63, 64, 67
- Commission shall adopt (rather than 'may' adopt) 32
- Scope should be better defined /detailed comments on scope 25, 58, 67
- The scope should not be defined in the legislation / leave the scope flexible 48, 51, 53, 56, 57
- This will support inspections and quality management /include quality management 23, 29, 30
- GVP should cover healthcare professionals. 7, 8, 12
- GVP should respect international agreements e.g. ICH 39, 48, 51, 53, 56, 57, 58, 67
- Develop GVP with ICH / respect international agreements 26, 39, 61, 64, 65
- ICH should not be involved / too much influence of industry 77
- Need clarity on whether Volume 9A will be retained and updated / if updated this needs to be timely and robust 30, 48, 50, 51, 53, 56, 57, 65, 67
- Include GVP in Volume 9A of Eudralex 25, 50
- Retain the current Volume 9A (updated as necessary) 30
- Replace current guidance with GVP (don't add) 48, 49, 51, 53, 56, 57, 67
- Clarify how GVP will be developed 39, 48, 50, 51, 53, 56, 57, 67
- Patients /healthcare professionals to be involved in development of GVP 2, 6, 8, 12
- Consultation should include industry 48, 51, 53, 56, 57
- Concern about adoption through comitology. 6, 39
- GVP should be a regulation not a guideline 48, 51, 53, 56, 57, 58, 63
- GVP should not be a directive 50
- GVP should be a directive 30
- How will EU GVP link to national GVP 30
- Concern re standard of current translation maintenance of terminologies 36

4.7 Overarching provision obliging the Member States to enforce penalties for non-compliance with PhV provisions [Dir 2001/83 Article 101o]
Supportive: 1, 14, 19, 20, 23, 29, 35, 77
- Penalties need to be real 77
- Penalties to include suspension of the marketing authorisation 1
- Penalties should not be detrimental to public health 20
- The type of penalties should be specified 20

- Need clearer definition of the Member State measures 48, 51, 53, 56, 57, 63
- Need clear processes 48, 51, 53, 56, 57
- Needs an appeal mechanism 48, 51, 53, 56, 57, 63
- Provisions need greater clarity / can one MS impose a penalty on a company established in another MS 58
- Need penalties for non-execution of post-authorisation studies 79
- Clear interface with Commission penalties / regulation 658/2007 needed 30

5. Rationalise informing the authorities about the company pharmacovigilance system and clearer inspection provisions, overall
Supportive: 5, 6, 14, 20, 22, 23, 24, 25, 26, 29, 30, 32, 37, 39, 42, 45, 47, 48, 49, 50, 51, 52, 53, 55, 56, 57, 58, 60, 61, 63, 64, 65, 67, 70, 71, 75,
Not supportive: 1, 7, 8, 12, 77

- Company pharmacovigilance system should be company specific and risk management plan should be product specific 23, 29
- Need transitional measures for implementation including for products with existing detailed descriptions / old products 39, 48, 51, 53, 56, 57, 63, 65
- The company and not the qualified person should sign that the applicant has the necessary means to fulfil the tasks 48, 51, 53, 56, 57, 58, 59, 67
- Do not have national variants 61
- Scope for international collaboration on the contents of the file 44
- Need to cater for the specificities of parallel importers 75

5.1 Define a 'pharmacovigilance system master file - PSMF' [Dir 2001/83 Article 1(34)]
Supportive 5, 8, 12, 28, 38, 47, 52, 58

- PSMF should be held by the EMEA (and MA application updated accordingly) 49, 50, 65
- EMEA should maintain closed database of qualified persons 57
- PSMF should not include internal audit reports only evidence that audit is conducted 48, 49, 50, 51, 52, 53, 55, 56, 57, 58, 65, 72

5.2 At application for Marketing Authorisation only submit a summary of the pharmacovigilance system and reference to the site of the PSMF [Dir 2001/83 Article 8(3)(ia)]

Supportive 23, 29, 48, 49, 51, 52, 53, 56, 57, 58, 64, 65
Not supportive: 1, 60, 28

- Maintain the detailed description concept / the PSMF is submitted to the competent authority annually 28, 30
- Submit key elements rather than a summary 30, 38, 49,
- Disconnect the PSMF from the marketing authorisation 33
- If the PSMF is submitted annually then future applications can refer to it 28
- Make clear that the site is a single site and is where the qualified person for pharmacovigilance resides 25, 48, 51, 53, 56, 57, 65
- Changes should be notified not a variation 49, 71
- Need clarity on what a summary entails 52,
- The summary can be in the PSMF 60
- Do not include qualified person contact details 31

5.3 Requirement for the PSMF to be maintained by companies [Dir 2001/83 Article 101l(4)]

Supportive 5, 23, 28, 29, 38, 47, 48, 49, 51, 53, 56, 57, 58, 64, 65

- Responsibility for management / archiving needs to be clearer (22)

5.4 Requirement for the PSMF to be submitted on request [Dir 2001/83 Article 23]
Supportive 14, 23, 29, 58, 64

- Clarify the timeframe 48, 51, 53, 56, 57, 65
- Large number of such files may need to be submitted to the authorities 38

5.5 Explicit reference to access to the PSMF during inspections [Dir 2001/83 Article 111]

Supportive 14, 23, 29, 58, 64

5.6 Pharmacovigilance inspection reports to be collated by the Agency and obligation on Member States to apply penalties. [Dir 2001/83 Article 111]
Supportive: 1, 25
Not supportive 35

- Need guidance on 'serious deficiencies' detected during inspections 39, 48, 51, 53, 56, 57, 63
- The legislation should clarify the process for the audit report and the MAH comments on it 48, 50, 51, 53, 56, 57, 63, 65
- Clarify interface with GMP inspections / provisions could be clearer 30, 48, 51, 53, 56, 57, 65
- EMEA to establish and maintain an inspections database with the data supplied by the Member States 25
- Notification system needs to be detailed 39
- Maintain Member States holding inspection reports and sharing on request 35
- Establish minimum inspection standards at EU level 35
- Need legal basis for preauthorisation pharmacovigilance inspections 35.
- Ensure the supervisory authority is also informed 30
- Member State concerned should be the one where the pharmacovigilance function is carried out 30
- Introduce a risk based pharmacovigilance inspection system 25
- Introduce Member State work sharing 33

5.7 For centrally authorised products, for the purposes of PhV inspections, the supervisory authority will be the MS in which the MAH qualified person resides [Reg 726/2004 Article 56, 57(1) (aa)
Supportive 25, 49
Not supportive 48, 51, 53, 56, 57, 58, 63, 64, 65

- Use the same concept regarding the mutual recognition and decentralised products 25, 30
- Supervisory authority to coordinate pharmacovigilance inspections 30
- Make the authority the one where marketing authorisation holder is registered 48, 63
- Make the authority the one where the main company pharmacovigilance function is located 48, 51, 53, 56, 57, 58, 64, 66, 72
- Need for flexibility 49, 64
- There is a need for guidance 48, 51, 53, 56, 57
- Once the authority is designated it should be fixed / difficulty to have fixed authority if the qualified person location dictates the Member State 46

6.0 Rationalise and strengthen risk management planning, overall
Supportive 2, 3, 4, 5, 6, 8, 11, 12, 16, 18, 19, 20, 23, 24, 25, 26, 29, 32, 35, 38, 39, 42, 45, 47, 49, 50, 58, 63, 64, 65, 66
Not supportive: 7, 77

- Post-authorisation safety studies / surveillance studies should be compulsory 79, 80
- Responsibility for the follow up of risk management plans needs to be clarified including for centrally authorised products / periodicity of follow up needs to be specified 24, 31, 32, 39, 44, 47
- Follow up should not be a task for the EMEA 31
- Need for harmonisation of Member State implementation of risk management whenever possible / need for one risk management plan rather than negotiating with individual Member States 4, 48, 49, 51, 53, 56, 57
- Risk management systems should emphasise collaboration with healthcare professionals 8, 12
- Include events monitoring as a risk management tool 18
- Active post-authorisation monitoring is particularly important for first in class medicines 19
- Need more post authorisation studies 26
- Risk management plans should be kept updated and the periodicity of this should take account of PSUR periodicity 23, 29
- Proposals will not be cost neutral 48, 51, 53, 56, 57, 63, 65, 66
- There is a need for good guidance with examples 48, 51, 53, 56, 57, 64
- Implementation of risk management actions should be in consultation with the Marketing Authorisation Holders 48, 51, 53, 56, 57
- Requirements for authorising medicines should be more stringent 77, 79, 80, 81
- Authorisation of medicines should not be earlier in product development 28, 30, 31, 39
- Active-controlled comparative clinical trials needed for marketing authorisation approval 79
- Risk management plans will be a cover for direct to consumer advertising 77,
- Risk management plans should be able to cover groups of products 35
- Need to cater for the specificities of parallel importers 75

6.1 Define RM System [Dir 2001/83 Article 1(34)]
Supportive 8, 12, 14, 39, 40

- Avoid using the duplicative /clarify terms risk management system and plan (use the term risk management activity) 25, 30, 32, 33, 34, 42, 47, 48, 49, 50, 51, 53, 56, 57, 58, 64, 65

6.2 Clarify the existing legal requirement to submit a RM System at the time of the MAA but it make for all applications and proportionate to risk [Dir 2001/83 Article 8(3)(iaa)]
Supportive 8, 12, 35, 39
Not supportive 36, 47, 48, 51, 53, 55, 56, 57, 63, 70,

- The provision on proportionality to risk needs to be clarified / include the list of product types from EMEA guidance / only submit if there is a safety concern 48, 49, 51, 52,53, 56, 57, 58, 64, 65, 67, 71,
- Suggest generics follow the originator / no RMP for old established products 36, 70
- Retain the concept of submission of an application "if applicable" 48, 51, 53, 56, 57
- Link to risks from all available information will limit the plans regarding unexpected ADRs / focus on unexpected ADRs 77, 79, 80

6.3 New requirement to annex the RM System to the marketing authorisation thereby making it legally binding, including any studies included therein [Dir 2001/83 Article 21]
Supportive: 1, 2, 3, 8, 12, 19, 20, 23, 29, 35, 39, 42, 47

- Annex a “Summary Table of the Risk Management Plan” to the MA 25, 65
- Develop guidance on the “Summary Table of the Risk Management Plan” 25
- Only annex critical public health elements / a summary / clearly define process 32, 42, 48, 51, 53, 56, 57, 72
- It is not always possible to comply with studies / studies may be difficult to conduct in practice 48, 51, 53, 56, 57
- Also annex the safety specification 35

6.4 Replacement of the current ‘exceptional circumstances MA’ [Dir 2001/83 Article 22] by 'intensively monitored products' to ensure robust follow up of all new innovative products
Supportive 47
Not supportive: 7, 8, 11, 12, 16, 23, 24, 25, 29, 30, 31, 32, 35, 39, 48, 51, 53, 56, 57, 65, 77, 79, 80

- Exception circumstances type authorisations should not become the norm 77, 79, 80
- Modify the conditional marketing authorisation not the exceptional circumstances MA. 23, 29,
- Clarify which parts of the MA are to be made public 48, 51, 53, 56, 57

6.5 Where a risk management plan includes a requirement for a post-authorisation safety study, enhanced safety reporting or conditions regarding the safe and effective use of the product, then the product is intensively monitored (on the intensive monitoring list)
Supportive, 1, 2, 3, 5, 11, 16, 18, 19, 20, 24, 25, 27, 32, 35, 38, 39, 42, 45, 47, 52,
Not supportive 33, 67

- Make the criteria narrower / clearer 24, 30, 34, 39, 48, 51, 53, 56, 57, 58, 61, 63, 66, 67, 72
- Have national intensive monitoring lists 11, 16
- Do not have national intensive monitoring lists 48, 51, 53, 56, 57, 52, 58, 63, 64
- All new products should be on the list / clarify if intention is all new products / apply to all new active substances 23, 29, 32, 34, 39, 47, 48, 51, 53, 56, 57, 63
- Clarify whether products can be included on the list whatever the authorisation type (normal MA, exception circumstances MA or conditional MA) 25, 39, 48, 51, 53, 56, 57, 58, 61, 63
- Need for explanation for stakeholders of the purpose of the list 23, 29, 48, 51, 53, 56, 57, 58, 64, 65
- Products should be added post authorisation / clarify 25, 47, 48, 51, 53, 56, 57, 58, 63
- The control of the list should be specified (there should be public consultation on it) / The rules / criteria for removal from the list need to be clear 32, 34, 38, 45, 47, 48, 51, 52, 53, 56, 57, 58, 61, 63, 64, 65, 66
- Periodicity of review of the list should be specified 48, 51, 53, 56, 57, 58, 63, 65
- The role of the Pharmacovigilance Committee for the list should be clarified 48, 51, 53, 56, 57
- Avoid the term intensive monitoring 47
- The statement on the summary of the product information should focus on newly authorised rather than intensive monitoring 48, 51, 53, 56, 57

- There should be no 'intensive monitoring' statement on the PIL 34, 42, 47, 48, 51, 53, 56, 57
- Label new products as being new for their first 2-years on the market 3
- Include pictogram / symbol / inverted black triangle in product information to identify intensively monitored products. 1, 34, 35, 58, 64, 75, 77, 79
- Biosimilars should be routinely included on the list 63

6.6 Fulfilment of conditions and assessment of data required for continuing the marketing authorisation of the intensively monitored product
Supportive 23, 29,

6.7 Removal from public intensive monitoring list when measures in the RM System are completed
Supportive 20, 23, 25, 29, 45

6.8 Legal basis for a Risk Management System for authorised products [Dir 2001/83 Article 101p]
Supportive 2, 3, 23, 25, 29, 32, 35, 38, 39, 45, 47, 48, 51, 53, 56, 57
- Ensure the contents are legally binding 23, 29,
- Clarify that the legal basis relates to product authorised before the entry into force of the legislation 30, 32, 48, 51, 53, 56, 57
- There should be no restrictions on requiring risk management plans 77

6.9 Match legislation to current practice with regard to taking action to protect the public if the risk benefit balance is not positive. Deletion of the concept of “normal conditions of use” and simplification of criteria to focus on benefit risk (deleting 'insufficient efficacy' as a sub clause) [Dir 2001/83 Article 116 and 117]
Supportive: 4, 60
Not supportive: 1, 7 11, 16, 17, 33, 37, 63, 65, 77, 79, 80
- Therapeutic efficacy and / or added value to be considered essential criteria for marketing authorisations 1, 7, 11, 17, 30, 31, 34, 77, 79, 80
- Deletion of therapeutic efficacy (even though it is a subordinate clause to benefit risk) could be misunderstood 44
- Retain the concept of normal conditions of use 48, 51, 53, 56, 57, 63, 65
- Deleting the concept of normal conditions of use needs clarification 72
- Explicit support for deleting normal conditions of use 30

6.10 Create a new tool whereby the Competent Authority may prohibit the supply of the product to new patients [Dir 2001/83 Article 117]
Supportive 19, 20, 23, 29, 35
Not supportive 48, 51, 53, 56, 57
- Unclear how Member states could do this / this provision needs to be clarified 31, 48, 49, 65

6.11 New obligation on MSs to ensure provisions are in place for the enforcement of risk management plans [Dir 2001/83 Article 127a]
Supportive 11, 35, 39
- Clarify the scope of these risk minimisation measures 39

7. Unambiguous legal basis for requesting PASS (post-authorisation safety studies) for authorised products and revised definition of PASS, overall:

Supportive: 1, 3, 5, 7, 8, 11, 12, 14, 16, 19, 20, 23, 24, 25, 26, 29, 35, 39, 45, 47, 48, 49, 51, 53, 56, 57, 64, 67, 72, 77

- Pharmacovigilance Committee should also have the power to require studies 1
- Companies should be able to take requests from the Member States to the Committee for a binding opinion 49
- The basis for requesting studies should be concern about safety and not only "serious safety concerns" 8, 20
- Serious concerns should be justified 49
- Clarify / define "serious safety concerns" 48, 51, 53, 56, 57, 58, 67
- Need clear criteria for requesting such studies 49
- Link the requests for studies to risk management planning 24, 39
- Support for the revised definition of PASS 8, 12, 20, 23, 29, 30
- Not supportive of revised definition of PASS 16, 77
- Broader definition of PASS suggested 17, 18, 47
- Narrower definition of PASS suggested 48, 49, 51, 53, 56, 57, 58, 63, 65, 72
- Alternative definition of PASS suggested 25, 37, 41, 72
- PASS definition should link to risk management planning 48, 51, 53, 56, 57, 67
- Include a definition of post-authorisation study 23, 29, 47
- PASS definition should clarify location of the study 48, 51, 53, 56, 57
- Studies should not have to be conducted in the EU 48, 51, 53, 56, 57, 58
- Do studies have to be in EEA? / requiring EEA studies not scientifically justified 67
- Protocol amendments should be assessed 30
- No such studies should be required of parallel importers 75

7.1 Justified written request from the competent authority which includes the objectives and timeframe of the study
Supportive 23, 29, 58

7.2 Marketing Authorisation Holder may request to present explanations within 30-days
Supportive 23, 29, 49

- Extend the deadline 49

7.3 Competent Authority withdraws or issues final requirement
Supportive 23, 29,

- Companies should have the right of appeal 49

7.4 Final requirement is included as a condition of the marketing authorisation
Supportive: 1, 3, 23, 29,

8. Oversight for non-interventional post-authorisation safety studies, initiated, managed or financed by the marketing authorisation holder, that involve collection of data from healthcare professionals or patients, overall.
Supportive 5, 8, 12, 14, 20, 23, 24, 26, 28, 29, 39, 40, 45, 47, 48, 49, 50, 51, 53, 56, 57, 58, 63, 64, 72

- Amend /review the definition of non-interventional trial in Directive 2001/20/EC / Include a definition of non-interventional study in the legislation 23, 24, 25, 29, 33, 39, 47, 48, 51, 53, 56, 57, 63, 72
- Include academic studies in the scope of oversight 30

- Concern about studies falling in the definition but about which the Marketing Authorisation Holder can't control the protocol e.g. academic run or pricing authority requested studies / studies requested by other authorities 48, 51, 53, 56, 57, 58, 64
- Clarify whether the requirements cover investigator sponsored studies 30, 48, 51, 53, 56, 57, 52
- Only allow studies that are in risk management plans 40
- Need to rationalise the oversight with the risk management planning procedures 24, 39, 67
- Restrict the oversight to those protocols included in risk management plans or requested by the competent authorities 23, 29, 47, 48, 51, 53, 56, 57, 58
- Need to clarify whether the oversight applies to studies to be performed outside the EEA / include non-EEA studies if these are in a risk management plan 48, 51, 53, 56, 57, 58, 72
- Make oversight lighter / clarified 23, 29, 57, 58, 63, 64, 67
- Concern about the impact / workload of the Committee 25
- There will be a need for detailed guidance 24, 39, 47, 63
- There is a need for greater harmonisation of assessment of study protocols 48, 51, 53, 56, 57
- The Committees role should not extend to oversight of interventional studies / trials 26
- Establish a requirement to register studies in a register / clarify the interface with the EUDRACT database 30, 39

8.1 Guiding principles: The act of performing the study shall not be promotional and payments shall be restricted to compensation
Supportive: 1, 3, 5, 23, 29,
- Extend these principles to all PASS 23, 29, 47
- Make the key principle that the study has a scientific objective 48, 51, 53, 56, 57, 52
- Clarify the meaning of promotional 58
- Some of the principles of Directive 2001/20 Article 3 should apply 30
- Ethics approval should be sought 30, 40

8.2 Oversight: Draft protocol submitted to competent authority (study in one Member State only) or Committee on Pharmacovigilance (study in more than one Member State), overall:
Supportive: 3, 26, 63
- Oversight should be performed at national level / key role for Member States 23, 47
- Allow Member States to adopt specific measures 47

8.2.1 Authority / Committee may object within 60-days if protocol considered promotional or to fall within the Clinical Trials Directive
Supportive 25, 49
- Add also if the design will not fulfil study objectives 30
- 60-days is too long 49
- Objection on clinical trial grounds should result in the clinical trials directive applying 48, 51, 53, 56, 57
- There should be an appeal procedure 48, 51, 53, 56, 57, 63

8.2.2 Authority / Committee may, with 60-days, give a recommendation “to be taken into account”
- Committee view on study design should be binding / clarify if the recommendation is binding 30, 32, 39, 79

- Give a deadline for the recommendation 48, 51, 53, 56, 57

8.2.3 Major protocol amendments notified

Supportive 63

Not supportive 30

- Amendments should be approved 30

8.2.4 Submission of study reports and adverse reactions specified in the protocol

Not supportive 73

- Final study reports should not be specified in the protocol as the study may be outside the EEA 48, 51, 53, 56, 57, 63
- Submit the final study report within 12-months of the last patient visit / set a deadline for submission 30, 48, 51, 53, 56, 57, 63
- Obligatory to submit final study report 30

8.2.5 Obligation to vary the MA if study results impact on labelling

Supportive 25

- Ensure variation to terms of the marketing authorisation if that is justified 25, 32
- Obligation on the company is not strong enough 77

8.2.6 Obligation to submit abstract of the study results to the Committee which may make this public and may make recommendations for the product labelling

Supportive 28, 48, 51, 53, 56,

Not supportive 49, 57

- Marketing Authorisation Holder should not have to agree to the amended abstract being made public 7, 8,12, 28
- Marketing Authorisation Holder should agree to any abstract being made public / should be consulted 48, 49
- Major work load 25
- Abstract submitted even if early study termination 32
- Submission of the abstracts should be electronic 25
- Submission of an abstract is insufficient 77

8.2.7 Committee recommendations for the labelling are made public and “shall be taken into account” by authorities and Marketing Authorisation Holder

Supportive 1, 48, 51, 53, 56, 57, 63

- Consult the Marketing authorisation holders on any recommendations 48, 51, 53, 56, 57, 63, 72
- The measures should be more robust / should be binding on the company 32, 39, 77
- Do these measures apply to single country studies 72

9. Strengthen and rationalise expedited single case adverse drug reaction reporting, overall

Supportive: 5, 6, 14, 16, 20, 23, 24, 25, 29, 32, 35, 38, 39, 42, 45, 48, 49, 50, 51, 53, 55, 56, 57, 58, 59, 62, 63, 64, 65, 67, 70, 71, 80,

- Important Member State role in ADR reporting / data quality / knowledge of local markets and prescribing practice / reporting should be first to national or regional centres to increase the quality of reports 11, 16, 23, 27, 29, 30, 32, 33, 35, 38, 39, 40, 47, 74
- National databases / national assessments of data are good for pharmacovigilance 47, 77
- Maintain the current balance between Member States and EMEA 25
- Need for a transition period 30
- Eudravigilance should be central to these plans 3, 65

- Concerns regarding the reliance on Eudravigilance / Eudravigilance yet to be proven 30, 35, 38, 47, 77
- Include specific methods for Member States to encourage healthcare professionals to report adverse reactions / concentrate on quality of reports from professionals 8, 12, 74
- Make reporting compulsory for healthcare professionals 11, 79
- Consider incentives on healthcare professionals to report 79
- Need legal obligation on the Member States and Marketing Authorisation Holders to ensure high data quality in Eudravigilance 25
- Data recording and processing rules are unclear 77
- Ensure exchange of drug misuse / abuse data with the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) and Europol 25, 78
- Reporting rules on companies should retain the concept of suspected / causality criteria proposed for reporting not supported / amendments proposed 5, 20, 23, 25, 29, 30, 31, 37, 39, 47, 48, 49, 50, 51, 53, 55, 56, 57, 58, 63, 65, 67, 72, 77
- Support for the causality criteria / there is need for causality criteria 62, 72
- Reintroduce reporting of suspected transmission of an infectious agent or include it in the definition of an ADR 25
- Enforcement will be important to ensure all Member States are compliant and no additional requirements are added at Member State level 48, 51, 53, 56, 57, 64, 65
- Clarify that solicited reports should not be recorded and submitted by the marketing authorisation holders 48, 51, 53, 56, 57, 58
- Marketing Authorisation Holders should not have to receive reports in E2B format / clarify the requirement for Marketing Authorisation Holders to accept reports electronically (from whom / role of E2B) 48, 49, 51, 53, 55, 56, 57, 65, 72
- Make all reports electronic / companies to receive reports electronically 26, 38
- ADR exchange between the agencies should be in a common format 10
- Marketing Authorisation Holders to ensure data 'accessible' rather than 'collated' at a single point in the Community 48, 49, 51, 52, 53, 56, 57, 58, 64, 65, 67, 72
- Embed ADR reporting in healthcare systems 6
- ADR exchange between the agencies / from companies should be in English only 10, 48, 51, 53, 56, 57, 58, 65, 67
- Ensure the flow of reports between stakeholders is crystal clear 49
- Ensure information on the degree of dilution of homeopathic products is captured 55

9.1 Simpler ADR reporting
Supportive: 3, 6, 10, 14, 16, 20, 23, 26, 29, 32, 35, 38, 39, 42, 45, 48, 49, 50, 51, 53, 55, 56, 57, 58, 59, 62, 63, 64, 65, 67, 70, 71
9.1.1 Obligation on the Agency, in collaboration with the MSs and Commission to have a European pharmacovigilance database and data processing network (Eudravigilance)
Supportive 2, 3, 6, 7, 24, 35, 39, 45, 58, 65, 67, 70, 71, 80
9.1.2 Eudravigilance allows all competent authorities to share/access information at the same time
Supportive: 3, 24, 35, 38, 39, 45, 48, 51, 53, 56, 57, 58, 65,
- Marketing Authorisation Holders also need access to the data (E2B compliant) / clarify MAH access 30, 39, 48, 49, 50, 51, 52, 53, 56, 57, 58, 63, 65, 67
- Must ensure access of national authorities to all the data / Member States must have full access to data need for pharmacovigilance 30, 33, 35, 38, 47

9.1.3 Marketing Authorisation Holders submit electronically all domestic EU adverse reaction reports to Eudravigilance

Not supportive 8, 12, 20, 30, 31, 35, 38, 42, 47, 48, 49, 51, 53, 55, 56, 57, 58, 59, 60, 61, 63, 64, 65, 67, 69, 70, 72, 73

- Do not expedite (i.e. no 15-day reporting) non-serious cases / have periodic reporting for non-serious cases 20, 25, 31, 32, 48, 49, 50, 51, 53, 55, 56, 57, 58, 59, 61, 63, 64, 65, 66, 67, 72, 73
- Support for reporting to Eudravigilance only / there should be no additional reporting to the Member States 48, 49, 50, 51, 53, 56, 57, 65
- Domestic EU reports should be submitted to the Member States 47
- Domestic EU reports should be sent to Eudravigilance plus country of origin 23, 28, 29, 30, 31
- Report also to the Reference Member State / Rapporteur country 31
- Non-serious clinical trial, PASS and solicited reports should not be expedited 48, 51, 53, 56, 57, 58, 63, 73
- Clinical trial reporting for authorised products should be simplified / should be the same as pharmacovigilance reporting 73
- Do not submit cases received from EEA authorities to avoid duplicates 48, 51, 53, 56, 57, 59
- Concern regarding costs of electronic reporting / have a waiver for parallel importers/ small companies 60, 75
- Only report serious unexpected ADRs 70
- Parallel importers to report to the originator company 75

9.1.4 Marketing Authorisation Holders submit electronically all serious non- EU adverse reaction reports to Eudravigilance

Supportive 20, 23, 28, 29, 35, 42, 47, 48, 49, 50, 51, 53, 56, 57, 58, 63, 64, 65

- Also report non-serious non-EU 35

9.1.5 Member States that receive reports submit them to Eudravigilance and MAHs

Supportive 48, 51, 53, 56, 57

- Member States should have a 15-day timeline imposed 48, 51, 53, 56, 57, 64, 65, 72
- Member States should validate reports before submission to Eudravigilance 48, 51, 53, 56, 57, 72
- Do not submit reports to MAH / MAH access via Eudravigilance 30

9.2 Patient reporting of adverse drug reactions, overall

Supportive: 1, 2, 3, 4, 5, 8, 11, 12, 16, 19, 21, 25, 28, 30, 32, 35, 39, 41, 42, 45, 49, 50, 51, 52, 53, 56, 57, 71, 72, 77, 79, 80, 81

Not supportive 15, 36

- Ideally patient reports should have medical confirmation before they are recorded and reported 38, 48, 49, 50, 51, 52, 53, 55, 56, 57, 65, 71, 72, 74
- The role of the healthcare professional in interpreting symptoms is important /professionals important for quality/ encourage dialogue 5, 15, 30, 38, 48, 50, 51, 52, 53, 55, 56, 57, 58, 65, 71, 74, 79, 80
- Need a variety of methods of patient reporting e.g. phone lines, websites etc 2, 11, 16, 35, 48, 50, 51, 53, 56, 57, 58, 65, 79
- Concern regarding the volume of reports 49, 58
- Include a toll free company telephone number 48, 51, 53, 56, 57, 58, 63, 64
- Suggest a pilot is conducted 36
- Involve patient associations 17
- Common approaches for handling patient reports including for signal detection need to be developed 23, 29,

- Need safeguards against inappropriate reports and duplicates 30, 48, 51, 53, 56, 57, 72
- Clarify who is responsible for translations 48, 51, 53, 56, 57, 58
- Report patient reports periodically with non-serious reports 50, 51, 53, 56, 57
- Need guidance for industry on handling patient reports 52, 61

9.2.1 For intensively monitored drugs information on reporting in the patient information leaflet

Supportive: 1, 3, 4, 5, 7, 8, 11, 16, 21, 35, 67

Not supportive: 30, 47

- Member States to encourage reporting particularly for intensively monitored products 48
- We should encourage reporting of serious adverse reactions 19
- Include report forms with medicines 79, 80
- Do not include reporting forms with the leaflet 21, 25, 48, 50, 51, 53, 56, 57, 58, 63, 64, 65, 75
- Include a statement in the leaflet of all products 21
- Patient reporting forms should be distributed by healthcare professionals 48, 51, 53, 56, 57, 64, 75
- Patient reporting should be via the web 30, 41, 42, 48, 51, 53, 56, 57
- Reports can go to the company local representative 48, 51, 53, 56, 57
- Include consent to disclose the information 48, 51, 53, 56, 57
- Link intensive monitoring to intensified reporting rather than reporting all ADRs 42

9.2.1.1 Patient reports should be sent to the Marketing Authorisation Holder and subsequently to Eudravigilance

Supportive 63

Not supportive 5, 11, 16, 23, 24, 27, 28, 29, 30, 34, 35, 36, 38, 39, 41, 42, 47, 75, 77, 79, 80

- Reports should go directly to the authorities or option for reports to go directly to the authorities (+/- the healthcare professional or patient organisation +/- via regional centre) 1, 3, 4, 7, 8, 11, 12, 16, 23, 24, 25, 27, 28, 29, 30, 31, 32, 34, 35, 38, 39, 41, 42, 47, 50, 58, 79, 80
- If MAH remains the recipient then MAH should inform the patient that the report has been submitted to Eudravigilance 5
- Would the company follow up with the healthcare professional? 44

9.2.2 For non-intensively monitored drugs, Member States offer website reporting.

Supportive: 4, 5, 11, 14, 16, 25, 42, 50

Not supportive 47

- Also need to accept paper reports. 4, 11, 16, 21, 50
- Role for patient organisations 4
- Set a deadline for the Member States to implement 65

9.2.3 Within 5-years the Agency in collaboration with the MSs to make available web-based structured reporting forms to facilitate electronic reporting to Eudravigilance.

Supportive 2, 3, 4, 6, 7, 8, 10, 12, 14

Not supportive 24, 35, 36, 39, 47

- Deadline too short 17
- Reports should be submitted via the national authorities / concern on quality 23, 24, 29, 35, 36, 39, 40, 72
- Clarify the language rules for the submission of ADR reports centrally 39

9.3 Delineated responsibilities for the Agency to monitor the scientific literature [Dir 2001/83 new Article 101e], overall

Supportive 5, 20, 29, 31, 35, 38, 39, 42, 48, 49, 50, 51, 52, 53, 56, 57, 58, 63, 65, 70, 71, 80

Not supportive 25

- Industry will need to have access to the reports identified /Eudravigilance will have to be reliable / in order that companies do not have to duplicate the scanning to satisfy non-EU requirements, the EMEA would need to make available the reports to Marketing Authorisation holders within short timeframes 30, 48, 50, 51, 52, 53, 56, 57, 58, 61, 65, 67, 72
- Scope for agreement with other international partners for products authorised outside the EEA / potential for deviation from ICH 44, 46, 48, 51, 53, 56, 57, 52, 65, 67
- Need to make clear the standards /methods for EMEA literature scanning 31, 35, 38, 48, 49, 50, 51, 53, 56, 57, 52, 63, 65, 71, 72
- Support for a guideline / industry has relevant experience to input into the guide 49
- Need transparency of the processes for the scanning / list the journals and the substances 44, 48, 49, 50, 51, 53, 56, 57, 52, 72
- Consider industry work sharing 25
- Consider public private partnership / subcontract the task 25
- Will the work be done by EMEA staff or work-sharing between the Member States /support for work sharing 28, 38
- Clarify whether the Marketing Authorisation holders will still be responsible for monitoring local medical literature / literature not on the EMEA list 28, 30, 35, 48, 51, 53, 56, 57, 52, 63, 67, 71
- Legislation should waive / does legislation waive any responsibility for screening from the marketing authorisation holder 30, 49, 60, 61
- Companies should still be responsible for screening and taking action 32
- Limit the EMEA responsibilities to old established drugs 48, 51, 53, 56, 57, 58, 63
- EMEA / Member States should not request specific literature searches from the companies 49
- This will require significant resource / how will this be funded 28, 30, 49, 58

9.4 Clarify medication error reporting [Dir 2001/83 new Article 1(11) and new Article 101e], overall

Supportive 27, 38, 40, 45, 47, 48, 51, 53, 56, 57, 58, 63, 65, 67, 70, 77, 82

- Medication errors in Eudravigilance may dilute the dataset / ensure medication errors are labelled as such 23, 29, 31, 34, 37, 39
- Member States should report medication errors resulting in an adverse reaction to Eudravigilance 48, 51, 53, 56, 57, 58
- Need to also report "near misses" that could have resulted in a serious adverse reaction 48, 51, 53, 56, 57, 58, 63, 82
- Only report medication errors resulting in a serious ADR should be reported 72
- Medication error reports should also be made available to the Marketing Authorisation Holders 58
- Define Patient Safety Authority 58
- Use this opportunity to introduce Medication Error Reporting Systems (MERS) 82
- MERS should be confidential, non-punitive, voluntary and independent 82
- Need legal codes to protect the reporter / allow anonymous reporting 47, 82,
- MERS should collaborate internationally / need to use consistent terminology 82
- Need for expert assessment of root cause analysis 82

- Need greater clarity on the scope of medication errors to be reported / greater clarity on respective roles and responsibilities 30, 38, 39, 67

9.4.1 Definition of an adverse reaction "A response to a medicinal product which is noxious and unintended" i.e. not only "at doses normally used in man"

Supportive 8, 11, 25, 27, 40, 45, 47, 62, 70

Not supportive 24, 30, 33, 34, 36, 37, 41, 55, 58, 65, 69, 75

- Maintain the definitions of unexpected adverse reaction and abuse (and define medical and medication errors) 11, 16, 17, 23, 29, 30, 31, 33, 36, 37, 38, 39, 47, 48, 51, 52, 53, 55, 56, 57, 58, 63, 65, 67, 69, 75, 77, 79, 80
- Do not define medication error 82
- Include a new definition of unlisted ADR 48, 51, 53, 56, 57
- Need a definition of serious ADR 30
- Include the disease in the definition 15
- Delete unintended so as to capture drug abuse 25
- Also include in the definition "off-label caused ADRs" 27
- Align definition with international agreements 48, 51, 53, 56, 57, 58, 63, 65
- Need clarity has to what is reported where / risk that the proposals for the definition change will cause confusion 82
- Liability issues for the companies 75

9.4.2 Member States to ensure that the competent authority for medicinal products notifies reports of medication errors to any national patient safety authority (and visa versa)

Supportive 77, 82

- Mechanisms of interaction / data exchange need to be clearer 82

9.5 Member States to ensure that biological medicinal products are identifiable

Supportive 50, 52

Not supportive 65

- Member State actions could lead to disharmony 48, 51, 53, 56, 57, 52, 63
- Pharmacovigilance Committee to make concrete proposals 48, 51, 53, 56, 57, 52, 63
- Distinct INNs for biosimilars could / should be adopted 48, 51, 53, 56, 57, 58, 63, 67
- Outlaw substitution of a biosimilar for the innovator biological medicinal product (unless doctors agreement) 48, 51, 53, 56, 57, 58, 63
- Identification of biologicals should include those not prescribed / dispensed (i.e. those administered or OTC) 48, 51, 53, 56, 57, 72
- Make clear that identification is by using the product name for reporting 50
- Include class specific pharmacovigilance / identification advice in the product information 52
- Reporting should be the same for all types of product 65
- MAHs should follow up reports for biologicals for the exact product 25

10 Rationalise periodic safety update reports (PSURs), overall

Supportive 8, 11, 14, 16, 18, 20, 20, 23, 24, 25, 27, 29, 31, 32, 33, 35, 38, 39, 42, 45, 47, 48, 49, 50, 51, 53, 55, 56, 57, 58, 63, 65, 67, 70, 71

Not supportive 27, 28

- Avoid repetition of information with risk management plans 23, 29, 39
- Link to risk management plans not always possible 23, 29,
- Link to risk management plans whenever possible 39, 45, 47, 48, 50, 51, 53, 56, 57, 58,
- The method to link to risk management plan needs to be clarified 39, 48, 58, 63, 65

- Introduce simplified PSURs (executive summaries) for old established products 48, 51, 53, 56, 57, 64, 65
- Move away from fixed times for submission to a risk-based approach for periodicity 50
- Amend the renewal provisions to be linked to date of first marketing rather than first authorisation to ensure renewal is based on market experience 23, 29, 32
- Rationalise the PSURs requirements at renewal 22, 23, 29, 30, 70
- Need to cater for the specificities of / exemption for parallel importers 75

10.1 PSURs to be an evaluation of the benefit risk balance and an assessment of all relevant data rather than presenting raw data.
Supportive 49, 50
Not supportive 40, 47
- Only conduct a benefit risk assessment if there is a change in the safety profile of the product 48, 51, 53, 56, 57
- Only include sales / prescription data that is relevant 48, 51, 53, 56, 57, 58, 65
- Only include relevant data 64
- Include the line listings 47

10.2 PSURs submitted electronically
Supportive 48, 50, 51, 53, 56, 57, 52,
- Need to define, test and implement a standard before the legal requirement to submit electronically / need to clarify what electronic means 48, 49, 51, 52, 53, 56, 57, 63, 65
- Clarify if / make clear that the submission is to the EMEA only 39, 48, 49, 50, 51, 53, 56, 57, 65
- Submission should be to the Member States where the product is authorised as well as the EMEA 30, 32, 36
- Submit to the Member State if only authorised in one Member State 31
- Only forward to those Member States where the product authorised 36
- Maintain the possibility of paper copies 30

10.3 Frequency and dates of submission rationalised, overall
Supportive 18, 22, 23, 24, 25, 27, 29, 32, 33, 35, 38, 39, 42, 47, 48, 49, 50, 51, 53, 56, 57, 58, 65, 67, 70, 71
- Allow the Marketing Authorisation 60 + 90 days from the data lock point for submission 48, 51, 53, 56, 57
- Ad-hoc requests for PSURs should give reasonable deadlines for their production / delete "immediately" on request / ad-hoc requests should have timeframes for submission defined 46, 48, 50, 51, 53, 56, 57, 72
- Use international rather than EU birthdates / take into consideration international birthdates 46, 48

10.4 No routine PSUR submission for generic, well-established use, informed consent, homeopathic, or traditional use registered herbal medicinal products, although PSURs may be specific condition of the marketing authorisation or requested by the Pharmacovigilance Committee
Supportive 18, 20, 23, 25, 27, 35, 38, 42, 47, 49, 55, 58, 67, 70
Not supportive 16, 28, 29, 31, 37, 48, 57, 65, 69, 77
- Clarify how old established products are defined / caution advised in defining old established products / if the derogation is maintained for old established products

then make it independent of the authorisation route (i.e. derogate for off-patent innovator products) 27, 28, 39, 47, 48, 49, 51, 53, 56, 57, 58, 61, 67, 71

- Companies should routinely produce PSURs for these products but only submit them on request or during inspection 20
- PSURs for generic products should still be written 30, 31, 37, 50
- If no routine PSURs then need more inspections 30
- Need for regular literature review and product information update 25, 30
- Exemption for old established products should extend to those authorised prior to the introduction of bibliographic applications (Directive 2001/83 Article 10a) 49
- Support continuing PSURs for all biologicals 51, 53, 56, 57, 52
- If no routine PSURs for old products then submission of usage data will be incomplete 37.
- Potential for deviation from ICH 46
- Suggest a study into the benefits of PSURs for established products 18

10.5 Committee on Pharmacovigilance to have key role, overall
Supportive 22, 23, 29, 35, 38, 39, 47, 48, 51, 53, 56, 57, 61, 70
Not supportive 25, 27

- Make the procedures / scope more precise 30, 39, 48, 51, 53, 56, 57, 61, 65
- Coordination should be by the CMDh 25
- Make the Committeee's role even more important 38, 61
- The proposal is more centralisation than work sharing 27
- This will be a major work load 39

10.5.1 Draw up public list of European reference dates for active substances
Supportive 22, 23, 29, 35, 38, 39, 49, 50, 61

- Dates should be specified by the Committee on Pharmacovigilance 22, 23, 29, 38, 39, 47, 58
- Base dates on existing work sharing lists from PhVWP / Heads of Agencies 48, 50, 51, 53, 56, 57, 58, 65, 67
- Base dates on first placing on the market not first authorisation 23, 29, 32
- If dates not known the Committee should be able to allocate any date 23, 29, 50
- Dates should be voluntary 49
- Clarify if new medicinal products will be caught or not 39

10.5.2 Receive requests from MAHs to change frequencies and dates

- No variation should be necessary 25
- No input from CHMP should be necessary 25
- Birth dates should not be changes / open to negotiation, only frequency of submission of PSURs should be negotiated 32, 50

10.5.3 Committee empowered to change frequencies and dates even if condition of the MA and to request PSURs even for generic etc. products
Supportive 23, 29, 35, 38, 48, 49, 50, 51, 53, 56, 57

- Make clear the power of the committee to fix and change submission dates for mutual recognition and de-centrally authorised products 48, 51, 53, 56, 57
- Need clear criteria for requesting PSURs / justify requests 49
- The periods covered by the PSUR dates and the deadlines for submission should be specified 50, 58

10.5.4 Appoints a MS or a rapporteur who produces an assessment report within 90-days MAH can comment on assessment report
Supportive 23, 29, 48, 50, 51, 53, 56, 57, 63
Not supportive 24

- Use existing CHMP Rapporteur or Reference Member State 24, 39
- Reduce the deadline (to 30 or 60-days) 25
- Base the procedure on that used currently for centrally authorised products 48, 51, 53, 56, 57, 58, 64
- Companies need more time to comment 46

10.5.5 MAHs and Competent Authorities to "take account" of the recommendations for the product information made public on the web portal
Supportive: 23, 29, 64

- Strengthen the wording in line with the proposals for Article 22, 23, 29, 32
- Competent Authorities should provide translations 50
- Need link to CMDh for implementation of recommendations for the product information 22

11. Strengthen transparency and communication, overall
Supportive: 1, 2, 3, 4, 5, 6, 7, 8, 11, 12, 14, 16, 19, 20, 22, 23, 24, 25, 28, 29, 34, 35, 39, 42, 45, 48, 50, 51, 53, 56, 57, 58, 60, 64, 65, 77, 79, 80, 81

- Make public more information on the benefits and risks of medicines / include efficacy and safety i.e. cover benefit and risk information / ensure information is explained and put in context / explain the rationale for decisions 1, 23, 29, 35, 48, 51, 53, 56, 57, 58, 65
- Proposals do not go far enough 34, 77, 79, 80
- Actively engage with stakeholders 3
- Create a stakeholders drug safety forum 3
- Inform healthcare professionals of safety issues before patients / work with healthcare professional groups on communications. 7, 8, 12
- Need stakeholder consultation on the implementation of these provisions 48 , 51, 53, 56, 57, 67
- Need consultation with the Marketing Authorisation Holder on the information to be made public for their products 48, 49, 51, 53, 56, 57, 67
- All confidential information should be protected not just commercially confidential 48, 51, 53, 56, 57
- Pharmaceutical wholesalers can play a vital role in distributing safety messages 54
- Companies should not be responsible for sending out safety messages / safety communications should be for the public authorities / less involvement of industry 77

11.1 Agency, in collaboration with the MSs and Commission to maintain a European medicines safety web-portal on the safety of medicines which will include links to websites of the Member State competent authorities. Overall:
Supportive: 2, 4, 5, 6, 20, 23, 25, 29, 35, 39, 42, 45, 47, 48, 51, 53, 56, 57, 58, 60, 65, 67, 80

- Need clarity on the companies responsibility for the information / clarify roles and timing 49, 66
- Need link to the Commission Sanco Public Health Portal 25
- Clarify the interface with / support for a link to Eudrapharm / have one comprehensive site for all medicines / information about benefit important / use European Public Assessment Reports 23, 25, 29, 39, 48, 57, 67, 72
- Clarify language issues / need translations 23, 29, 30, 36, 39
- Ensure resources available to perform this task 25
- Ensure information submitted to EMEA electronically by industry to reduce workload 25, 57

11.2 List of information to be made public via the web-portal, overall
Supportive: 1, 2, 6, 23, 25, 29, 42
- Signal should be made public / signals should be notified to healthcare professional organisations / clarify if signals made public 7, 34, 39, 77
- Need clarity on whether information on signals is made public (a working group with stakeholders is suggested) 23, 29,
- Include medicines consumption data 1
- Include a list of prohibited medicines (referred to in the current Article 123 of the Directive) 8, 9, 77, 80
- Include a list of medicines temporarily suspended 8, 9, 12
- Include requests of studies 77, 80
- Include companies responses to requests 77, 80
- Executive summaries of evaluation reports should be made public 30, 39
- Publish committee assessment reports / summaries of assessment reports 28, 39, 42
- Include key warnings / key safety information / new warnings 39
- Needs greater clarity 36

11.2.1 Information on the committees
Supportive 57, 77
- Provisions should go much further 77, 80
- Publish the involved experts 39

11.2.2 Information on how to report ADRs
Supportive: 1, 2, 3, 4, 6, 23, 29, 71
- Information in all EU languages. 4
- Reminders to patients to consult their doctor 48, 51, 53, 56, 57, 67
- Include link to national reporting sites 36, 47

11.2.3 Agreed risk management plans
Supportive 18, 20, 32, 34, 35, 39, 41
Not supportive 40
- Concern about releasing assessments and plans 31
- Needs greater clarity 39
- Patient orientated summaries should be made public / key elements 32, 48, 49, 50, 51, 53, 56, 57, 58, 67
- Just publish lists of agreed plans 40
- Marketing authorisation holders should agree the information 48
- Confidential information should be deleted 48, 51, 53, 56, 57, 63
- Proposals do not go far enough 34, 77
- Ensure safety specifications are made public 35

11.2.4 Intensive Monitoring List
Supportive: 1, 5, 25, 39, 42, 77, 80
Not supportive 27, 30

11.2.5 MAH qualified persons and the MS where they reside
Not supportive 32, 48, 49, 50, 51, 52, 53, 55, 56, 57, 58, 63, 64, 65, 67, 72
- Clarify the purpose of this public list 39, 72

11.2.6 PSUR reference dates and assessment conclusions and recommendations
Supportive: 1, 23, 29, 32, 47, 48, 51, 53, 56, 57, 58, 63, 64, 72
- Concern about releasing (full) assessments / interim conclusions 31, 47, 67
- Make PSURs public / make PSUR conclusions public 1, 40, 77
- Make the assessment report (summary) public 23, 29, 32, 39,

- Make public final assessment report conclusions in lay language 48, 51, 53, 56, 57, 58, 64
- Information should be put in the context of benefit 48, 51, 53, 56, 57
- There should be consultation on the information made public 48, 51, 53, 56, 57
- Consider including the information in the European Public Assessment Report 48, 51, 53, 56, 57, 72

11.2.7 PASS protocols, abstracts and recommendations

Supportive: 1, 34, 57, 58

Not supportive 49

- Publish summaries only 58
- Need a deadline for the protocols to be added 30
- Create a study registry compatible with WHO-network 57
- No not publish PASS protocols 48, 51, 53, 56,
- Interface with EUDRACT needs to be clarified 24
- Requests to be made public 1
- Company response to be made public 1

11.2.8 Information on referrals and public hearings [Dir 2001/83 Articles 101k]

Supportive: 1, 6, 20, 24, 39, 42

Not supportive 36, 48, 49, 51, 53, 56, 57

- There should be flexibility about when public hearings are organised / make them possible rather than obligatory 24, 38, 39, 42, 47
- Public hearing should be possible for other committees and for non-safety issues 24
- Public hearings will be resource intensive 23, 25, 29, 32, 36, 39, 42, 47
- Without interpretation the benefit for most citizens would be limited 36
- Support for use of web-based hearings 23, 29,
- Need to clarify the aim of public hearings 25, 30, 32, 33, 48, 51, 53, 56, 57, 64
- Marketing Authorisation Holders should be systematically invited to any hearings 48, 51, 53, 56, 57, 63, 64, 67
- Marketing Authorisation Holder should be informed before any public announcement 48, 51, 53, 56, 57, 58, 64, 65
- Clarify the procedures 65

11.3 Member States to have national medicines safety web-portals linked to the European portal

Supportive: 4, 6, 23, 29, 32, 36, 39, 80

- Ensure method for EMEA to establish standards for the Member State websites 58
- Ensure information on ADR reporting 36, 39
- Use European Public Assessment Reports 72
- Include a deadline 65

11.4 Clear Provisions on transparency relating to Eudravigilance [Dir 2001/83 Articles 101d(3)]

Supportive: 1, 2, 6, 23, 28, 29, 35, 40, 41, 42, 50, 77, 80

Not supportive 48, 51, 53, 56, 57

- Provide information in aggregated tabular format /need to have proactive provision of aggregated data by the EMEA 25, 32, 42, 47, 48, 51, 53, 56, 57, 77
- When supplying data in will need to be explained / put in context 29, 40, 42, 65, 72
- Citizens to access the data via the National Competent Authority 48, 51, 53, 56, 57
- Need EU wide access policy (with requests going through EMEA) 23, 28, 29, 35, 65, 72

- Do not release individual case safety reports to the public 48, 51, 53, 56, 57, 63, 65
- Release of reports to the public should respect confidentiality and data should be put in context 48, 50, 51, 52, 53, 56, 57, 58, 65, 72
- When product specific data is released the company should be informed 48, 51, 53, 56, 57, 72
- The benefit of such transparency is questioned 49, 52, 58
- Make Eudravigilance easily accessible for consumers 1, 6, 77, 80
- Release PSUR assessment reports rather than individual case safety reports 48, 51, 53, 56, 57
- Supplying data should attract a fee 40
- Maintain the current legislative proposals 47
- Need to assess the impact of / work load from the proposals 25

11.5 Greater EU coordination of communications about major safety issues [Dir 2001/83 Articles 101i], overall
Supportive: 3, 5, 7, 8, 12, 23, 29, 35, 39, 48, 49, 50, 51, 53, 56, 57, 58, 63, 64, 65, 66, 67
11.5.1 As soon as an MAH has the intention to make a public announcement relating to important PhV concerns, authorities must be notified
Supportive: 4, 23, 29, 47
- Current proposal is unclear / concept of 'intention' is unclear 48, 51, 53, 56, 57
- This provision should be further strengthened 4, 23, 29, 47
- Deadline of 48-hours suggested 23, 29,
- Limit notification on withdrawals to those for safety reasons 48, 51, 53, 56, 57, 63

11.5.2 Obligations on the MSs, Agency and Commission to give each other 24-hours notice of public announcements “unless urgent public announcements are required for the protection of public health”
- No comments received

11.5.3 Strengthened coordinating role for the Agency for important safety messages relating to substances authorised in more than one MS: common safety messages and distribution timetables
Supportive 5, 35, 49, 50, 58, 64, 65, 67
- Member States to agree common safety messages / make all reasonable efforts to agree common messages 48, 50, 51, 53, 56, 57, 58, 64, 66
- Provide one single contact point for the Marketing Authorisation Holder (EMEA, Rapporteur or the Reference Member State) 48, 51, 53, 56, 57, 64
- Create an obligation on the authorities to consult the marketing authorisation holder 48, 51, 53, 56, 57, 58
- Need to clarify the role of the EMEA c.f. the role of the new pharmacovigilance committee / c.f. Member States 23, 29, 39
- Member States may need to amend messages / cultural factors / national laws 23, 29, 35, 36, 39
- Not all Member State communications are appropriate for EU coordination 23, 29, 35, 36, 39
- Role of the EMEA should be administrative / supporting 47
- Harmonisation in urgent situations may be very complex 29, 39
- Clarify how this will work 39

11.6 Clear legal provisions on the provision of medicinal product information to support the development of EudraPharm and the EU PhV medicines terminology [Reg 726/2004 Article 57(2)], overall.

Supportive 5, 25

- Needs greater clarity /does this refer to submission of Summaries of Product Characteristics and Patient Information Leaflets or a drug dictionary 48, 50, 51, 53, 56, 57
- Work should be consistent with developing a global drug dictionary / consistent with the ICH M5 standard 48, 51, 53, 56, 57, 58, 64, 65, 67
- Limit the scope to marketed products 48, 51, 53, 56, 57, 67
- Prefer to link the provision of data to the Eudravigilance Medicinal Product Dictionary not Eudrapharm. 25
- There is a need for a terminology covering herbal and homeopathic substances 55
- Contradiction with Article 57(1) of Regulation 726/2004 which precludes the industry being involved in the updating and management of Eudrapharm.25
- Any data fields from trials should be consistent with WHO data fields 58, 64
- Concern for effective implementation of these provisions / need for guidance 63

11.6.1 Within 6-months the agency makes public a format for electronic submission of medicinal product information and within 18-months all MAHs electronically submit medicinal product information for all their products

Not supportive 48, 51, 53, 56, 57

- National competent authorities should submit the data and companies validate it 48
- Make the deadline longer 48, 49, 51, 53, 56, 57, 65

12 Strengthen product information, overall

Supportive: 3, 5, 6, 8, 11, 12, 14, 16, 18, 20, 21, 22, 23, 25, 26, 28, 29, 31, 32, 35, 36, 38, 42, 48, 51, 53, 56, 57, 58, 67, 68, 70, 81

Not supportive 32, 39, 49, 59, 67, 77

Note: the feedback on the intensive monitoring statements is in section 6

- Have a key information summary rather than just safety information section / include a summary which should include what the medicine is for / put safety messages into the context of the benefit/ concern about affects on compliance 21, 22, 23, 25, 29, 33, 37, 42, 47, 48, 49, 50, 51, 53, 56, 57, 58, 63, 64, 65, 66, 67
- Needs implementation work / guidance to ensure the work is done well / consistently and for clarity on when and how /need to define key 18, 21, 22, 23, 25, 29, 35, 36, 37, 38, 42, 43, 48, 49, 50, 51, 52, 53, 56, 57, 58, 63, 64, 65, 66, 67, 68, 70, 71, 72
- Need a long implementation phase flexibility i.e. not just renewal or next major variation / clarify the implementation 37, 48, 49, 51, 53, 56, 57, 63, 65
- Create a new summary document specifically for healthcare professionals and subject to regulatory scrutiny 20, 22, 30
- Need to review the structure of product information overall / make better use of the existing product information 24, 34, 35, 39, 48, 51, 53, 56, 57, 58, 67, 68
- Include the dosing information in the key information 31
- Highlight new information 77
- Use alert cards 39
- Use IT systems to highlight information 39
- There will be associated costs 49, 60, 65
- Need a working group to recommend on product information 35
- Support improving the readability using the current structure 28, 30
- Need clarity on whether products with a well established and very high level of safety need ‘key safety warnings’ 23, 29,
- There is a clear link to the work of the Pharmaceutical Forum and the Commission's ‘information to patients’ proposals 2

- Include a message to discuss side effects with the doctor / pharmacist 8, 12
- Different safety knowledge categories suggested 19, 20
- Any changes should be subject to testing / clarify the testing rules 48, 49, 51, 52, 53, 56, 57, 58
- Key safety information should not include detailed information on risk minimisation measures 48, 51, 53, 56, 57
- Product information must be updated rapidly with new information on adverse reactions 81
- It is a right to receive accurate up to date information 81

12.1 Summary of Product Characteristics to include new section on key safety information about the medicinal product and how to minimise risks. For intensively monitored medicines this would include adverse reaction reporting information. [Dir 2001/83 Article 11]
Supportive: 3, 14, 20, 26, 31
Not supportive 24, 59
- Specific proposal for reorganisation of section 4 of the SPC / detailed drafting comments 67
- Include boxed warning at start of SPC / after Section 4,2 on posology 26, 68
- Include the new section in Section 4 of SPC 43

12.2 Outer / immediate packaging of intensively monitored medicines to state "All suspected adverse reactions should be reported (see leaflet for details)". [Dir 2001/83 Article 54]
Supportive 14, 65
Not supportive 48, 51, 53, 56, 57, 59, 63, 67, 75
- Use big font 14
- Include 'road signs' / Pictogram to see the leaflet 14, 25, 58, 64, 75, 77, 79

12.3 Packet leaflet to include new section on key safety information about the medicinal product and how to minimise risks. For intensively monitored medicines this would include adverse reaction reporting information. Information to be presented in a box surrounded by a black border. [Dir 2001/83 Article 59]
Supportive: 1, 3
Not supportive 24, 30, 59, 60, 77
- Use bold text rather than black box / do not use a black box 21, 48, 51, 53, 56, 57, 59
- Place the summary at the beginning of the leaflet 21
- Proposals on organisation of information within the current PIL format 21, 68
- Black box may be helpful 58
- Black box could be confusing 64
- Include ADR frequencies in the leaflet 1
- Give leaflets to hospitalised patients. 3

13 Other major comments not covered in points one to twelve above.
- Need greater EU coordination of Pharmacovigilance 3, 5, 6, 8, 10, 12, 51, 53, 56, 57, 65
- Need more harmonisation between the Member States 3, 48, 49, 51, 53, 56, 57, 65
- Member States have an established and important role in pharmacovigilance / there is a need for more emphasis on monitoring at a national level 9, 11, 16, 27, 33, 35, 77

- Maintain strong national accountability and responsibility / respect national sovereignty 33, 67
- Pharmacovigilance is an important public health issue / focus needed on medication safety 1,2,3, 6, 7, 8, 10, 11, 12, 14, 16, 23, 24, 29, 55, 77, 79, 80
- Ensure implementation of safety warnings in product information including leaflets is streamlined / link to variations regulations/ update of PSMF by notification /including outcomes of referrals/ including PSUR outcomes / ensure updates are only Variation Type 1A 22, 30, 32, 48, 49, 50, 51, 53, 56, 57, 63, 64, 65, 71
- Use the WHO definition of pharmacovigilance 41
- Proposals are threat to public health / patient protection is weakened 77, 79, 80
- Condemnation of the Commission for the proposals 77
- Proposals will expose patients to less well tested medicines 77, 79, 80
- There is a need for independent safety studies and independent research / need for public funding. 1, 6, 11, 16, 19, 23, 29, 47, 77, 79
- Need clarity on funding on safety studies 35
- Community framework programmes / public funding should support specific drug safety studies 1, 23, 29,
- Community framework programmes should support research into the methodology of pharmacovigilance 1
- Support for a pharmacovigilance / pharmacoepidemiology network 10, 23, 25, 29, 63
- Create the legal basis for the EMEA to establish and maintain a European pharmacoepidemiology network 25
- There is a need for public education campaigns /stakeholder involvement to raise awareness about the importance of ADR reporting / medicines safety. 1, 2, 6, 8, 11, 12, 14, 16, 19, 20, 48, 51, 53, 56, 57, 71
- Patient associations can play a key role in training and education 2
- There is a need for measures to reduce the harm from medicines well established in medical practice which cause well known toxicity 19
- Competence for medicines and pharmacovigilance should be moved from the European Commission DG Enterprise and Industry to DG Health and Consumer Protection. 1, 16, 79
- Make centralised system obligatory for all medicines 1
- Make reference to Article 3(1) of the Treaty "a contribution to the attainment of a high level of health protection" 2
- Commission to fulfil its remit to protect citizens under Article 125 of the Treaty 77
- Make reference to pharmacovigilance as a patients' right 2
- There is a need for an EU law to allow citizens to bring legal action for damages caused by action or omission of companies of medicines authorities / this should be a right of citizens need new mechanisms to provide for liability 81
- ICH is too influential / industry is too involved at ICH 77
- Increase collaboration with international partners/ there is a need for more international collaboration 3, 48, 51, 53, 56, 57, 61, 63, 64, 65, 67
- Support for greater EMEA involvement in international harmonisation and standardisation / ensure international harmonisation and collaboration is pursued 23, 29, 58, 63, 64, 65
- Create clearer Support for EMEA/EU liaison with WHO 23, 29, 48, 51, 53, 56, 57
- Benefits of the strengthening will be felt beyond the EU 45
- Major benefit from the opportunity to discuss future proposals for legislation changes 45

- Patient and healthcare professional associations have an important role in pharmacovigilance 10
- There should be more emphasis on the role of pharmacists 7, 8, 9, 12, 13, 14
- Include responsibility for environmental consequences of medicines in the remit of the new pharmacovigilance 10
- Over the Counter (OTC – non-prescription) medicines need robust pharmacovigilance 9, 12, 13, 14
- Pharmacovigilance should cover homeopathic medicines 10
- Need to clarify the role of practitioners of complementary and alternative medicine in pharmacovigilance 10
- There is a need to consider the specifics of homeopathic and anthroposophic medicinal products 55
- Clarify whether advanced therapy medicinal products are covered by the proposals 23, 29,
- During implementation there will be a need for joint industry and regulators training 49
- There is a need to revise existing guidelines on parallel imports and distribution 52
- Opposition to direct to consumer advertising (note: outside the scope of this proposal) 81
- Clarify whether investigational medicinal products are covered by the proposals 23, 29
- Calls for rationalisation of clinical trials safety reporting 26
- Regional centres are important 11, 12, 41
- Overall the proposals will increase the workload on Member State authorities 29
- Include GCP and PhV inspections as possibilities during the assessment of MA applications 32
- Pharmaceutical wholesalers can play a vital role in product recalls consider an EMEA lead product recall system including the EU wholesaler network 54
- Parallel importers should not have all the main pharmacovigilance requirements applied to them / requirements should be proportionals75
- Respect national business law 67