



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

GVP - Key themes from the public consultation and next steps

Guideline on good pharmacovigilance practices (GVP)
Comments from “first wave” public consultation

Presented by: Priya Bahri (EMA) on behalf of the GVP Team

An agency of the European Union





EUROPEAN MEDICINES AGENCY

Public consultation February – April 2012



P Bahri: GVP 1st wave public consultation themes and next steps

Participating organisations

- 14 pharmaceutical industry organisations
- 37 individual pharmaceutical companies / consultancies
- 2 service provider associations for industry
- 1 patient organisation
- 4 healthcare professional organisations
- 1 learned society or similar
- 2 academic/training organisations
- 1 public –private partnership
- 4 individuals (2 physicians, 1 academic)
- 9 Member States
- 3 international organisations



Thank you!

General comments

- Appreciation for extensive, comprehensive and overall well-written guidance
- Difficult consultation due to ongoing development of Implementing Measures
- Difficult distinction of legal terms “shall” and “should” for non-native English speakers
- Difficult consistency and coherence checks due to staggered release of GVP Modules
- Inconsistencies within and between some Modules
- Inconsistency in application of definitions
- Appreciation for consistency with requirements elsewhere for advanced therapy medicinal products
- Limited guidance on process-specific quality management
- Some spelling, grammar and punctuation errors and impaired readability



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Implementation timelines





M I - Pharmacovigilance systems and their quality systems

General comments:

- Broad support for quality systems
- Appreciation for detailed and helpful guidance
- Concern over burden, in particular for smaller companies, with a request for a proportionate approach
- Request for some clarifications and details
- Out-of-scope comments relating to legislation



M I - Pharmacovigilance systems and their quality systems

Specific comments regarding requirements for all organisations:

- Appropriate pharmacovigilance training of all personnel in accordance with role
- Concerns over formality training checks
- Requests to specify “all documents” in relation to record management and retention requirements
- Requests to specify requirements for adequate document controlling of the quality system
- Requests for illustrating examples and clarifications regarding facilities and equipment subject to quality management.



M I - Pharmacovigilance systems and their quality systems

Specific comments regarding requirements for MAHs:

- Pharmacovigilance system master file (PSMF) to be regarded as quality manual
- Where evidence is known to exist, but is not available to a MAH, e.g. because it is owned by a third party which is not willing or able to share it with the MAH, the MAH should only have to provide a brief explanation as to why the data are not available.
- Concern that the public may become aware about assessments and recommendations published on the European Medicines Web-Portal before the MAH with request to provide MAHs with direct ("sign-up-for" automatic) notifications.



M I - Pharmacovigilance systems and their quality systems

Specific comments regarding requirements for the qualified person responsible for pharmacovigilance in the EU (QPPV):

- Request to specify which QPPV can be delegated
- Divergent views over the QPPV role in relation to validation of ADR database
- Difficulties in early QPPV involvement in portfolio enlargement / contractual arrangements due to confidentiality



M I - Pharmacovigilance systems and their quality systems

Specific comments regarding requirements for competent authorities:

- It remains open how competent authorities will guarantee independence.
- Competent authorities should follow-up ICSRs notified to them by primary reporters and transmit this information to MAHs.
- Only transfer of phv tasks to another competent authority is considered appropriate (not to a commercial organisation).
- The public should be informed which phv tasks have been transferred.
- Delegation of phv tasks from one Member State to another may result in one Member State becoming extremely influential; limitation in delegations to be discussed.



M II - Pharmacovigilance system master file (PSMF)

Comments (1/2):

- Request for clarifications regarding transitional arrangements in relation to phv system summary and variations
- Concerns over PSMF maintenance/change control/logbook/PSMF Annex regarding administrative burden and the resource implications, in particular for smaller companies
- PSMF maintenance/change control/logbook/PSMF Annex: The requirement for detailed lists to be maintained in the different PSMF sections is seen as a burden, if not moved to the Annex.
- PSMF Annex should be that part of the PMSF that contains those components which will be subject to continuous updating.



M II - Pharmacovigilance system master file (PSMF)

Comments (2/2):

- For those components of the PSMF that derive information from company controlled systems that are validated and have an associated audit trail, the source of the history of change should also be derived from the controlled system and not be duplicated in the PSMF.
- Request for clarifications on PSMF registration process and PSMF location when the PSMF is electronic
- Request for clarifications on PSMF maintenance in cases of sub-contracting and shared PhV systems
- QPPVs' concerns of disclosure of addresses

M V - Risk management systems

General comments:

- Many organisations felt that risk management plans (RMPs) should not be requested for every medicinal product.
- Request for proportionality of RMPs for different product types
- Request for use of language from the legislation – efficacy vs effectiveness
- Request for more guidance on the selection of safety concerns (i.e. not every ADR)
- Request for template
- Comments regarding similarity/overlap/differences with PSURs
- Concern over transitional arrangements

M V - Risk management systems

Comments regarding pharmacovigilance plan (PP):

- Question whether use of specific follow-up forms should be categorised as a routine or additional activity
- Question whether study protocols or proposals should be included in the annex and whether these should be in English
- Comment that proposal that “studies which might provide useful safety information” should be included in the PP is too broad
- “Generic companies shouldn’t have to do studies”
- Comment that promotional studies should never happen as they are unethical
- Relationship between the Quality of Opinions exercise and what is included in the PP

M V - Risk management systems

Comments regarding educational material:

- Many comments on educational material for generics relating to:
 - Access to educational material of originator
 - Whether copyright or intellectual property issues would permit generics to make their educational material similar to that of the originator
 - Whether generic companies could pay a fee to originator companies and use the same material
 - Whether generic companies should provide it at all

M V - Risk management systems

Comment from a patient organisation:

Very strong comment that it was inappropriate to include details of the race of patients when tabulating characteristics of patients in clinical trials:

- “Concept of race is not driven by science but racism”
- Argument that race is not an important determinant of genetic polymorphism and hence pharmacokinetics.
- “Should suggest genetic testing for all patients if a particular polymorphism is important”



M VI – Reporting of individual case safety reports (ICSRs)

- Follow-up reports: The request for confirmation in writing of details given verbally will not be workable in practice because it will be overly burdensome for MAH and HCPs, even if pre-populated forms are used to reduce burden. Should be proportionate to the risk.
- Internet: Recommendations that MAHs should actively monitor special internet sites such as those of patient's support or special diseases groups, which are not under their management or responsibilities, in order to identify significant safety issues, would constitute a significant bureaucratic burden. It is unlikely to result in improved public health protection. There are risks of duplicate reporting. Such data should be used as an adjunct to conventional spontaneous adverse event collection and not entered into the company safety database.
- Market research programmes: Guidance on handling ICSRs from market research programmes should be included.



M VI – Reporting of individual case safety reports (ICSRs)

- Comparator reporting: Clarify the reporting requirement for the situation where the ADR originates from a clinical trial in EU, when the reaction is suspected to be related only to another authorised medicinal product taken concomitantly, which is not part of the clinical trial protocol, and which does not follow the definition of Non-Investigational Medicinal Product (NIMP). This case should be considered a spontaneous report. It sometimes happens that a serious ADR occurring with a marketed product being an IMP or a non-IMP during a clinical trial sponsored by another company is made available to the MAH of the marketed product. Should the MAH submit this case with its product in EudraVigilance database ? Only if a SUSAR ? Never?
- ICSRs from PASS: Collection of non-serious ICSRs from post-authorisation studies does not generate any relevant safety information. These cases are present in the study database and are summarised in a final report. Huge workload and duplication of actions needed for these solicited non-serious reports.



M VI – Reporting of individual case safety reports (ICSRs)

- Reporting from class action lawsuits: Include guidance on what level of information is expected to be included in ICSRs in the scenario where hundreds of pages are provided to the MAH on one patient. Are MAHs expected to trawl medical records for any adverse reaction associated with the drug or just those adverse reactions which are being alleged in the lawsuit? Request an exemption for follow-up reports of up to 60 days for a company that has received a large batch of legal cases, consistent with the situation in the US.
- EudraVigilance: Request for details for the requirements for the MAH to download ICSRs from EV. How reports received directly by MS will be actively shared with concerned MAHs in final arrangements? How would MAHs get these reports into their pharmacovigilance database? Is it the MAHs responsibility to review EV periodically and to find any company product reports they do not already have? Expectations on this process should be detailed.



M VI – Reporting of individual case safety reports (ICSRs)

- Case narrative: Case summaries should be limited to the information that has not been included in the structured fields. All coded information should not be repeated in narrative, especially when the time sequence is possible to read out of the structured data. The case narrative should describe data/time sequence that add value to the structured data. It is common practice in industry that no or abbreviated case narratives in line with CIOMS V are written for non-serious expected safety reports to make efficient use of available resources and to focus on important safety information. Is still acceptable?
- EU privacy law: Due to differing and ever changing requirements throughout the EU, it would be helpful if member states compiled an appendix highlighting which member states have data protection laws different to the ones established by the EU directive on data protection. HMA could lead on such an initiative.



M VI – Reporting of individual case safety reports (ICSRs)

Reporting from the literature: The requirement to submit literature cases from country where a company holds a MA but has never commercialised the product should be removed. Increases duplicate reporting by different MAHs. As regards exclusion for articles which present patients in tables/line listings: If all criteria for a valid case are present, but only in the table/line listing format, it is assumed this does not need to be reported? For period between the application and granting of MA, the monitoring of literature should be done periodically but not on a weekly basis. More guidance for when MAH cannot exclude the product on the basis of territory: If MAH has supplied products to territories where it does not hold a MA, these ICSRs should be captured and reported appropriately. Articles in non EU languages. Can day 0 be considered as the date by which the translation becomes available to MAH/third party. More protection of MAHs needed re copyright issues when handling of electronic copies of articles. When submission of a PDF is not allowed for reason of copyright, it should be stated that a literature reference will be acceptable.



M VI – Reporting of individual case safety reports (ICSRs)

- Reporting during public health emergency: Very similar to language set out in section 5.12 of Vol 9A. Industry experience during the 2010 pandemic was that this language was entirely without use or effect. Agencies appeared powerless to amend the reporting requirements notwithstanding the provisions in 5.12 of Vol 9A. Contrast the proposed approach in the EU with the approach in the US. In the absence of an agreed international approach the US guidelines alone are unlikely to be helpful in the event of an emergency.

M VII – Periodic safety update report

General comments:

- General concerns about if non-EU countries will accept the new PSUR format and content.
- Interface between the GVP module and the ICH-E2C (R2); concerns expressed regarding the timeliness for the finalisation of the ICH-E2C guideline.
- Comments regarding the overlapped information with the RMP and DSUR.
- The new PSUR format is considered by some stakeholders very extensive and complex, especially the benefit-risk evaluation and therefore it is challenging for MAHs to adapt their systems to this new report.
- General GVP structure (A, B, C) was not properly understood in some cases.
- Different clarifications requested for the transitional period regarding the implementation of the new format and content.
- Also clarifications requested for the submissions of PSURs for nationally authorised products (MRP/DCP) until the EU single assessment is implemented.

M VII – Periodic safety update report

Comments regarding the PSUR content (1/2):

- Line listings of individual cases:
 - Line listings will not be routinely included in the PSURs and stakeholders requested further clarifications for this topic in relation also to the reporting requirements to EudraVigilance.
- Case narratives and non-serious cases:
 - Stakeholders suggested clarifications for the request established in the Implementing Regulation on the inclusion of case narratives.
 - Concerns regarding how regulators will address lack of data about non-serious cases in the transitional period for ADR reporting.
- PSUR Reference Information and updates of the Product Information:
 - Clarifications requested regarding the PSUR Reference Information and the requirements in the PSUR regional appendix related to the Product information. Special concerns for the nationally authorised products (MRP/DCP) in the context of the EU single assessment.

M VII – Periodic safety update report

Comments regarding the PSUR content (2/2):

- EU marketing authorisation status:
 - Stakeholders challenged the request in the PSUR Regional Appendix for the EU marketing authorisations status and expressed the difficulties to gather the data requested.
- Estimated exposure and use patterns:
 - Different stakeholders expressed the challenges for the presentation of the subject/patient exposure as suggested in the Module.
- Literature:
 - The guidance provided in this section were considered very prescriptive and not applicable to all products.
- Signals and risk evaluation:
 - General clarifications requested regarding the different information presented in the 4 different sub-sections of this PSUR section.

M VII – Periodic safety update report

Comments regarding the process (1/2):

- EURD list:
 - Clarifications requested about when the list will take effect and how often is going to be updated.
 - The inclusion in the EURD list of PSURs request from competent authorities is well accepted and regulators are encouraged to use the EURD list for predictability.
 - Comments regarding variations to the marketing authorisation requirements according to the EURD list and submission of applications for modifications of the EURD list by the MAHs
- Products under the routine exemption of PSURs submission:
 - Different clarifications for the waiver in the legislation for the obligation to submit PSURs routinely for generic medicinal products, well-established use medicinal products, homeopathic medicinal products and traditional herbal medicinal products.

M VII – Periodic safety update report

Comments regarding the process (2/2):

- Submission of PSURs on demand of a competent authority:
 - Clarifications requested regarding the interpretation of DIR Art 107c(2) “Marketing authorisation holders shall submit PSURs immediately upon request from a competent authority in a member state”
- MA Renewals:
 - Comments and uncertainties for the “non-submission” of PSURs, summary bridging reports and addendum reports at the time of the renewals of Marketing Authorisations.
 - Stakeholders suggested a transitional period for the new renewal submission requirements

M VIII – Post-authorisation safety studies (PASS)

General comments:

- Definition of PASS: to be clarified that PASS are defined by their primary objectives (many studies have safety as 2nd/3rd objective)
- Many divergent comments on the definition of non-interventional studies (note: text agreed with EC)
- Concerns over financial impact for smaller and generic companies
- Roles and responsibilities to be better defined (amend QPPV's sign-off of protocol or add possibility to delegate)
- Questions regarding transitional measures
- Need for harmonisation with FDA's guidance

M VIII – Post-authorisation safety studies (PASS)

Comments regarding structures and processes:

- Scope to be better defined, e.g. interaction with risk mgt systems, studies conducted outside the EU, studies conducted by 3rd parties on behalf of MAH
- Request for clarification as regards obligation vs. recommendation
- Clarification needed on transmission of study information
- Useful proposals on formats of study protocol and final study report
- Need for clarification on situations where a waiver to submit a final study report within 12 months would be acceptable
- Request that end of data collection as a milestone to count the 12-month timeline for submission of final study report should include data validation



M VIII – Post-authorisation safety studies (PASS)

Comments regarding operation of EU network:

- Request for procedure to discuss need for study with MAH before imposition
- Clarification requested on procedure for imposing PASS for mutually recognised/decentralised medicinal products
- Request to involve patients' organisations in procedure for imposing PASS if they brought safety signals to regulators
- Joint studies should be a recommendation, not an obligation
- Comments regarding PRAC Rapporteur
- Comments and proposals for concomitant submissions of PASS final study report and variation
- Questions on operation of the PASS registry

M IX – Signal management

General comments:

- Appreciation for high level quality and completeness
- Appreciation as helpful guidance on activities related to safety signals
- Add advice on how to address signals arising from outside EudraVigilance
- Define signal communication in more detail

M IX – Signal management

Comments regarding roles and responsibilities:

- Clarify who is responsible for detection, assessment and, if applicable, removal of double reports on the level of the EU-database
- MAHs should be notified of validated signals sent to PRAC, of who the Rapporteur is, of timeframes and results of signal confirmation
- Request for specification of data sources to be monitored by MAHs
- Clarify if the MAH should notify as emergency safety issue only those signals that have been confirmed, rather than those that have been detected and are still under investigation or those that have been evaluated and did not suggest a new causal association

M IX – Signal management

Comments regarding signal detection, validation, analysis, prioritisation, assessment and tracking:

- Periodicity of data monitoring in EV: monthly or every 2 weeks considered excessive
- Add advice on how to address signals arising from outside EudraVigilance
- Provide recommendations for types of signal tracking system to be used by MAH
- Clarify what is expected to be captured in the audit trail
- Define how, when and what about the public will be informed about signals and assessment outcomes
- Request for signal reporting template

Annex I - Definitions

General comments:

- Appreciation for overall high quality, practical organisation and completeness
- Recognition as supporting the operations of pharmacovigilance
- Appreciation for consistency with internationally/globally agreed definitions (ICH, CIOMS)Difficult consultation due to ongoing development of Implementing Measures
- Comments on definitions which have already been/are currently subject to public consultation in the framework of development of legislation and ICH Guidelines

Annex I - Definitions

Comments for revision of definitions or explanatory notes:

- Occupational exposure: clarify that exposure may also relate to components of the medicinal product rather than to the product itself and to confirm that non-professional care activities are included
- Target population (treatment): give clarifications in relation to contraindications
- Medication error: specify the standard against which the error occurs and to include near misses
- Individual case safety report: specify that for a valid ICSR contact details should be available for the reporter to be considered as identifiable



Annex I - Definitions

Comments for adding definitions:

Active substance	Additional pharmacovigilance activity
Generic medicinal product	Routine risk minimisation activity
Traditional herbal medicinal product	Additional risk minimisation activity
Homeopathic medicinal product	Expedited report/reporting
Well established use	Stimulated report/reporting
Adverse reaction occurring in a clinical trial	Post-authorisation study
Unlisted adverse reaction	Post- authorisation efficacy study
Adverse event of special interest	Interventional study
Causality assessment	Cohort event monitoring
Designated medical event	Prescription event monitoring
Lack of efficacy	Registry
Vaccine failure	Data-mining
Low responder to vaccine	Proportional reporting ratio
Off-label use	Incident
Compassionate use	Emerging safety issue
Drug diversion	Efficacy
Routine pharmacovigilance activity	Effectiveness



Next steps



GVP Modules – 1st wave

I PhV Systems and their Quality Systems

II PhV System Master File

V Risk Management Systems

VI Individual Case Safety Reports

VII Periodic Safety Update Reports

VIII Post-Authorisation Safety Studies

IX Signals

→ Final (drafts): June 2012

GVP Modules – 2nd wave

IV Inspections

X Additional monitoring

→ Public consultation launch: mid June 2012

GVP Modules – 2nd wave

III Audits

X Additional monitoring

XV Safety communication

→ Public consultation launch: mid July 2012

GVP Modules – 3rd wave

XI Public participation

XII Continuous phv, benefit-risk evaluation, communication planning and decision-making for regulatory action

XIII Incident management

XIV International collaboration (tbc)

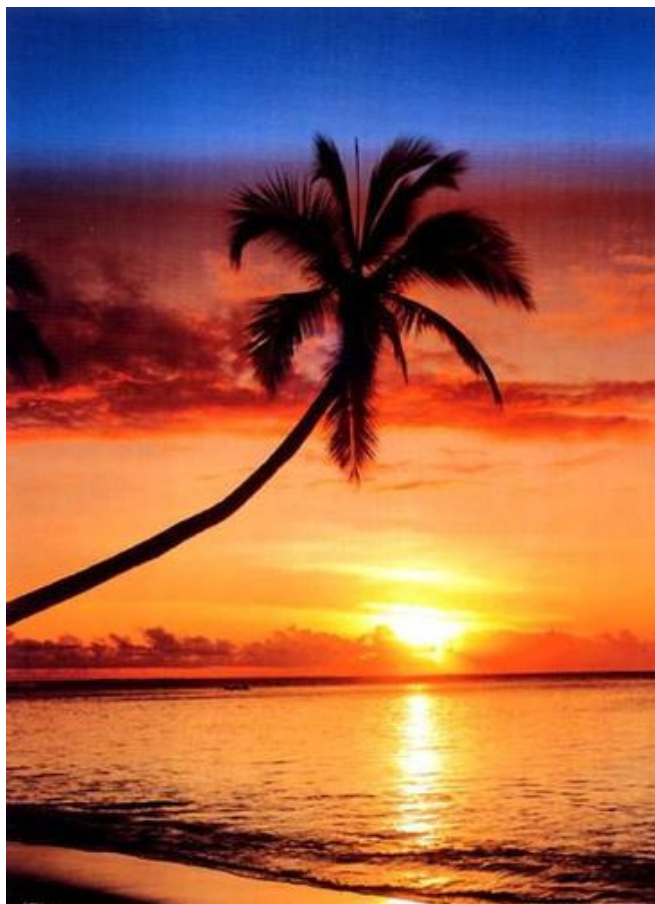
XVI Risk minimisation measures

→ Public consultation launch: staggered Q3/4 2012



GVP Considerations for product- and population-specific pharmacovigilance

- Biological medicinal products
- Vaccines
- Pregnancy
- Children
- Elderly
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Thank you for your
continued
participation in the
upcoming
consultations.