EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Good pharmacovigilance Practices (GVP) – Module P-II Biological medicinal products

4th industry stakeholder platform - operation of EU pharmacovigilance legislation – 12 June 2015

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Disclaimer

GVP Module P.II. is a work in progress.

The orientations presented in this presentation may change following consultation of EMA Committees and the public consultation.

Content of presentation

- Definitions
- Objectives
- Scope
- Challenges associated with pharmacovigilance for biologicals
- Overview of guidance
- Outcome of consultation on concept paper
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Biological medicinal product ('biological'): medicinal product that contains an active substance that is produced by or extracted from a biological source and that needs for its characterisation and the determination of its quality a combination of physio-chemical-biological testing, together with the production process and its control. [Directive 2001/83/EC, Annex 1, Part I, Art 3.2.1.1]

Similar Biological Medicinal Product ('biosimilar'): biological medicinal product that contains a version of the active substance of an already authorised original biological medicinal product (reference medicinal product) in the EEA, and which has shown similarity to the reference medicinal product in terms of quality characteristics, biological activity, safety and efficacy based on a comprehensive comparability exercise. (Guideline on Similar Biological Medicinal Products)

Related biological medicinal product: for the purpose of this Module and to distinguish them from biosimilars, a product which contains the same or closely related active substance as (an)other authorised medicine(s) but was not authorised as a biosimilar.

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- To explain the specific issues and challenges associated with pharmacovigilance for biologicals (**P.II.A**)

- To provide guidance on addressing these challenges when developing and implementing pharmacovigilance for biologicals (**P.II.B**)

- To provide guidance related to operation of the EU network, esp. roles and responsibilities of various stakeholders (marketing authorisation holders, national competent authorities, European Medicines Agency, PRAC) (**P.II.C**)

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GVP applies to biologicals, biosimilars and related biological medicinal products, which may encompass a very wide array of medicines, including

- Medicinal substances derived from blood and plasma
- Biotechnology-derived medicines
- Vaccines
- Advanced therapy medicinal products (ATMPs)

Prophylactic vaccines and ATMPs covered by specific guidance and not within scope of P.II

GVP P.II. supplements (and does not replace) other GVP Modules

Other specific guidelines to be followed, e.g.

- *Guideline on Similar Biological Medicinal Products*
- *Guideline on Plasma-derived Medicinal Product*
- *Guideline On Immunogenicity Assessment Of Biotechnology-Derived Therapeutic Proteins*
- *Guideline on Comparability of Biotechnology-derived Medicinal Products After a Change in the Manufacturing Process*
- *Guideline on Similar Biological Medicinal Products Containing Biotechnology-derived Proteins as Active Substance: Non-clinical and Clinical Issues*

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1. Immunogenicity

- More complex nature and higher potential risk of immunogenicity that could result, on rare occasions, in serious and life-threatening reactions
- Sources of immunogenicity are multifactorial and may involve:
    - product-related factors (e.g. cell line, impurities)
    - treatment-related factors (e.g. route, dosing frequency)
    - patient/disease-related factors (e.g. genetic background, concomitant medications, immune status)
- Consequences may include partial or complete loss of efficacy due to neutralising antibodies, altered pharmacokinetics, general immune effects such as anaphylaxis or cross-reactivity.
- Immunogenicity cannot always be reliably predicted or evaluated pre-authorisation, therefore greater uncertainty to be reflected in RMP and to possibly require specific surveillance post-authorisation.

2. Manufacturing variability

- Frequent changes to manufacturing process of biologicals post-authorisation
- The originator, biosimilar and related biological product may exhibit different safety profiles through their life-cycle
- Importance of continuous PhV and risk management activities
- Regulation (EU) No 1235/2010, Recital (17): "*Risk management plans are normally required for (…) a significant change in the marketing authorisation, including a new manufacturing process of a biotechnologically-derived medicinal product*."
- What does "significant" mean?

3. Stability and cold chain

- Non-adherence to manufacturing processes and standards, appropriate storage/handling conditions, cold chain and good distribution practices may affect stability and quality of biologicals and introduce immunogenicity and contamination.
- Importance of pharmacovigilance at batch-level.

4. Product traceability

- Product and batch traceability of biologicals is critical in clinical use
- Batch traceability is important following significant change to manufacturing process
- "*Member states shall ensure, through the methods for collecting information and where necessary through the follow-up of suspected adverse reaction reports, that all appropriate measures are taken to identify clearly any biological prescribed, dispensed or sold in their territory which is the subject of a suspected adverse reaction report, with due regard to the name of the medicinal product (…) and the batch number*" [DIR Art 102e]
- Challenges of batch traceability are acknowledged

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P.II.B.1. **Risk management system**

P.II.B.1.1. RMP part I “Product overview”

P.II.B.1.2. RMP part II “Safety specification”

P.II.B.1.2.1. RMP module SVII “Identified and potential risks”
and RMP module SVIII “Summary of the safety concerns”

→ Guidance of GVP Module V (RMP) to be followed

→ Same risks for biosimilars and related biologicals as for the originator, unless justified

→ Immunogenicity to be listed only if concern arises from evaluation

P.II.B.1.3. RMP part III “Pharmacovigilance plan”

P.II.B.1.3.1. RMP part III section “Routine pharmacovigilance activities”

P.II.B.1.3.2. RMP part III section “Additional pharmacovigilance activities”

→ Alignment of a additional PhV activities for biosimilars and related biologicals to originator product unless justified

→ Joint studies or registries are encouraged if applicable and feasible

→ After change of manufacturing process, emphasis on batch-related PhV for a certain period

→ Continuous monitoring of immunogenicity (principles of existing guidelines to be followed)

P.II.B.1.4. RMP part V “Risk minimisation measures”

→In principle, same for biosimilars and related biologicals as for originator

→May include educational material and measures to improve traceability, incl. SmPC wording

P.II.B.1.5. Updates to RMP due to manufacturing changes

P.II.B.1.5.1. Significance of a manufacturing change

No strict guidance on what may constitute “significant” change; evaluation based on:

- Nature of the change
- Comparability exercise

P.II.B.1.5.2. Risk analysis and further procedure

- All manufacturing changes should trigger risk analysis on potential significance and need for RMP update
- If need for RMP update concluded by MAH → updated RMP submitted in parallel with submission of variation to the manufacturing process
- Otherwise risk analysis to be submitted and assessed with variation
  - If RMP update needed → competent authority may provide recommendations on RMP
  - RMP update to be approved before marketing of changed product.

P.II.B.2. Management and reporting of adverse reactions, including product traceability

→ see GVP Module VI

P.II.B.3. Periodic safety update report

P.II.B.3.1. PSUR section “Estimated exposure and use patterns”

→ information as complete and detailed as possible re. product, batches sold/delivered and their distribution

P.II.B.3.2. PSUR section “Overview of signals: new, ongoing, or closed” and “Signal and risk evaluation”

→ following significant change to the manufacturing process, PSURs should specifically evaluate reports or any other information that might indicate a new clinical risk to a process change

P.II.B.4. Signal management

→ see GVP Module IX

→ at the product and substance levels and , if feasible and relevant, at batch level

→ system to be sensitive to detection of new risks arising from changes in quality

→ specific activities to be described in the RMP

P.II.B.5. Additional monitoring

→ see GVP Module X

P.II.B.6. Safety communication

→ challenges due to complexity of products and need to build/maintain public confidence

→ traceability

→ biosimilars

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Informal consultation of companies on concept paper in June 2014

Main comments addressed

Scope

1. Vaccines should be out of scope → agreed
2. Scope to small molecule medicinal products derived from biological sources? → ref. to legal definition

Risk management plan

3. Concern that Module P.II. would add regulatory burden based on theoretical risks

   → Guidance of Module V to be followed

4. Proposal that potential risks could be removed from RMP if no longer considered necessary → Guidance of Module V to be followed
5. Should risk of lack of efficacy be included in RMP and the strategy to assess it be made mandatory? → forthcoming PAES guidance; no mandatory strategy
6. Update of RMP following significant manufacturing changes: request on explanations on what constitutes “significant” + examples → significant changes to be assessed on a case-by-case basis; examples might be misleading

PSURs

7. Question about usefulness of including in PSURs information on numbers of batch numbers sold per region/country and how this information will be used; proposal is made that such information should be included only if relevant for the evaluation of safety.

   → Comment taken into account and explanations provided; however, information on batch distribution per country/region should be collected and compiled routinely.

ADR Reporting and monitoring

8. Need for risk-based approach for monioting of DR reporting frequencies; added value of continuous (weekly) disproportionality analyses unclear

   → Legislation: continuous and risk-proportionate PhV; clarifications in GVP P.II.

9. Information on batches difficult to obtain and HCPs do not report it

   → Acknowledged, but fundamental point of the legislation; clarification in GVP P.II.

10. Need for guidance on reporting of adverse events with/without brand names or lot numbers

    → Reference to GVP Module VI

Testing of immunogenicity

11. Question about methods for testing of anti-drug antibodies in practice; need for new research methods in collaboration with competent authorities

    → Reference to Guidance on assessment of product immunogenicity; working parties to be consulted.

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- General presentation to 4th Industry forum: 12 June 2015
- Draft discussed by Project Maintenance Group 1: 19 June 2015
- Consultation of PRAC, CHMP, CMDh, PhVIWG, BWP, BPWP, BMWP, CAT: starts end of June
- Public consultation: Q3 2015
- Finalisation and publication: Q1 2016