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Management and reporting of adverse reactions to medicinal products – Good Vigilance Practice Module VI

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Topics

- Scope of Good Vigilance Practice Module VI.
- Structure of Good Vigilance Practice Module VI.

- Requirements for collection and reporting of suspected adverse reactions in EU.
- Requirements for the electronic exchange of safety information in EU.

- Reporting modalities during transitional arrangements.
- Reporting modalities during final arrangements.

GVP Module VI: Scope

Title IX of Directive 2001/83/EC and Chapter 3 of Regulation (EC) No 726/2004

- Legal requirements on collection, data management and reporting of suspected adverse reactions associated with medicinal products for human use authorised in the European Union (EU) reported by healthcare professionals, patients or consumers.

Good Vigilance Practice Module VI (GVP VI)

- Guidance on implementation of legal requirements and existing guidelines applicable to competent authorities in Member States (NCAs), Marketing Authorisation Holders (MAHs) and the Agency.

GVP VI replaces Volume 9A:

- Chapter I.4: Requirements for expedited reporting of ICSRs,
- Chapter I.5: Requirements for reporting in special situations,
- Chapter II.1.3: Management of spontaneous reporting programmes,
- Part III: Electronic exchange of pharmacovigilance information in EU.

GVP Module VI: Scope

GVP VI provides also recommendations regarding the reporting of suspected adverse reactions occurring in special situations:

- Obligations of the applicant in the period between the submission of the marketing authorisation application and the granting of the marketing authorisation,
- Obligations of MAH following suspension, revocation or withdrawal of a marketing authorisation,
- Reporting in the event of a public health emergency,
- Reporting following the use of a medicinal product during pregnancy or breastfeeding,
- Reporting when a medicinal product is supplied in the context of compassionate use or named patient use,
- Reporting of suspected transmission via a medicinal product of an infectious agent,
- Reporting of lack of efficacy or of suspected adverse reactions related to quality defects or falsified medicinal products,
- Reporting of cases arising from class action law suits.

GVP Module VI: Structure

Section A: Introduction

- Regroups definitions relevant for the purpose of GVP VI which should be applied to Section B and Section C, issued from
  - Art 1 Dir. 2001/83/EC, ICH E2A and E2D guidelines;
  - Commission Implementing Regulation on the Performance of Pharmacovigilance Activities Provided for in Reg. (EC) No 726/2004 and Dir. 2001/83/EC;
  - Experts from Member States and Agency in dedicated working groups.

Section B: Structures and Processes

- Highlights internationally agreed principles in relation to the collection, validation, management and reporting of suspected adverse reactions to medicinal products.
- Issued from ICH E2A and E2D guidelines.

GVP Module VI: Structure

Section C: Operation of EU Network

- Presents EU specific requirements as defined in Reg. (EC) No 726/2004 and Dir. 2001/83/EC in relation to suspected adverse reactions to medicinal products for human use authorised in EU.
- Should be applied together with definitions and recommendations presented in Section A and B.
- Underlines distinctions with safety reporting rules applicable to clinical trials conducted in accordance with Clinical Trials Directive 2001/20/EC: No reporting under both regimes!
- Requirements specific to NCAs in order to encourage reporting from healthcare professionals, patients and consumers.
- Requirements specific to MAH in EU in relation to medicinal products for which they hold ownership outside EU, including
  - Those owned by organisations from same group of companies, or
  - When having concluded contractual agreements with other companies.

GVP Module VI: Structure

Appendixes

- Detailed guidance on the monitoring of scientific and medical literature, developed by the Agency [Reg Art 27(3)];
- Detailed guidance on the nullification of cases;
- Business process maps and process descriptions in relation to
  - Identification of biological medicinal products (name & batch #),
  - Modalities for expedited reporting during interim and final arrangements,
  - Transmission and rerouting to NCAs of ICSRs submitted to EudraVigilance by MAHs in final arrangements,
  - Transmission of ICSRs to WHO collaborating centre,
  - Data quality monitoring of ICSRs transmitted electronically,
  - Duplicate detection and management of ICSRs.

GVP Module VI: Main aspects

Collection and Reporting : Suspected adverse reactions

- NCAs and MAHs should take all appropriate measures in order to collect and collate
  - All reports of suspected adverse reactions to medicinal products
    - Independently of their condition of use (overdose, misuse, abuse, medication error, occupational exposure)
    - From unsolicited or solicited sources (spontaneous reporting, post authorisation studies).
  - Pharmacovigilance system structured in way that allows for reports of suspected adverse reactions to be validated in timely manner and exchanged between stakeholders within legal expedited time frame (including cases received outside EU by organisations belonging to same group of companies or by contractual partners).

GVP Module VI: Main aspects

Collection and Reporting : Suspected adverse reactions (Contd.)

- Only valid cases of suspected reactions qualify for expedited reporting. 4 minimum criteria need to be present:
  - 1 or more reporter(s), 1 patient, 1 or more suspected medicinal product(s), 1 or more reaction(s).
  - Only reactions (diagnosis and/or signs and symptoms) should be reported. No event.
    - Reasonable possibility of causal relationship between a suspected medicinal product and a noxious or unintended response (harm to patient), which arises from the medicinal product [Dir Art 1, ICH E2A];
    - Spontaneous reports are cases of suspected adverse reaction since convey suspicion of primary source, unless specifically stated by reporter [ICH E2D];
    - Solicited reports: only cases of reactions, where possible relationship between an event and a suspected medicinal product is considered by reporter or sender (MAH/NCA).

GVP Module VI: Main aspects

Collection and Reporting: Post-Authorisation studies

- MAHs record all reports of suspected adverse reactions (EU/non-EU) occurring in post-authorisation studies [Dir. Art 107(1)]:
  - Organised data collection schemes initiated, managed or financed by MAHs and which do not fall under scope of Clinical Trials Directive 2001/20/EC;
    - Non-interventional studies, compassionate use, named patient use, patient support and disease programmes, registries, surveys, information gathering on efficacy or patients' compliance.
  - MAHs should have mechanisms in place to collect full and comprehensive cases information at time of initial reporting to allow meaningful assessment of cases and expedited reporting of valid ICSRs to NCAs/Agency as applicable; (does not apply to study designs based on secondary use of data).

GVP Module VI: Main aspects

Collection and Reporting: Post-Authorisation studies (Contd.)

- For non-interventional studies
  - Non-interventional studies with primary data collection directly from patients or healthcare professionals:
    - Report only valid ICSRs where possible relationship between an event and a suspected medicinal product considered by reporter or MAH.
  - Non-interventional study designs based on secondary use of data (e.g., observational cohort studies):
    - Reporting is not required; events/reactions summarised in final study report.
- For compassionate use, named patient use, patient support programmes or other organised data collection schemes not under scope Dir 2001/20/EC:
  - Report only cases of reactions where possible relationship between an event and a suspected medicinal product considered by reporter or MAH.

GVP Module VI: Main aspects

Collection and Reporting: Literature monitoring

- Agency shall monitor selected medical literature for reports of suspected adverse reactions to medicinal products containing certain active substances [Reg. Art 24].
- MAHs shall only submit ICSRs published in scientific and medical literature for those journals and active substances not monitored by Agency.
- Until lists (journals & active substances) are published by Agency, MAHs should monitor all their active substances by accessing widely used systematic literature review and reference databases.
- Exceptions for not reporting ICSRs:
  - Where ownership of medicinal product by MAH can be excluded based on active substance name, formulation, route of administration, primary source country or country of origin of reaction;
  - Literature articles presenting summary data analysis from publicly available databases or detailing patients in tables or line listings;
  - Literature articles based on analysis from NCAs databases in EU.

GVP Module VI: Main aspects

Collection and Reporting: Emerging safety issues

- Events/observations which do not fall within the definition of valid ICSRs are not subject to expedited reporting requirements.
- Some of them may affect risk-benefit balance of medicinal product:
  - Major safety findings from non-clinical studies, non interventional post authorisation studies or clinical trials,
  - Safety issues arising from signal detection or literature monitoring, related to use outside marketing authorisation, due to misinformation in product information, in relation to supply of raw material,
  - Withdrawal, non-renewal, revocation, suspension of marketing authorisation or urgent safety restriction outside EU,
- Notified immediately as Emerging Safety Issues to concerned NCAs & Agency;
- Document should indicate points of concern and actions proposed for marketing authorisation/application.

GVP Module VI: Main aspects

Electronic exchange of safety information in EU

- Reporting of valid ICSRs electronically by NCAs and MAHs is mandatory for all medicinal products authorised in EU. Non-adherence constitutes non-compliance with EU legislation.
- Technical tools (EVWEB) available to SMEs to facilitate compliance with electronic reporting requirements.
- Applicable guidelines, definitions, internationally agreed formats, standards & terminologies, relevant for the electronic exchange of ICSRs in the EU and for the electronic submission of information on medicinal products to the Agency should be adhered to by all stakeholders.
- Complete information of a valid ICSR available to sender should be reported in structured and consistent manner in relevant ICH E2B data elements and in narrative section.

GVP Module VI: Main aspects

Electronic exchange of safety information in EU (Contd.)

- Processing of personal data in EudraVigilance is possible while respecting EU legislation in relation to data protection.
  - Use of pseudonymisation where information related to personal data cannot be transferred to EudraVigilance based on national legislation. E.g. replace name/address with pseudonym or key code.
    - Without impairing the information flow in EudraVigilance and interpretation and evaluation of safety data relevant for the protection of public health.
    - Patient's age, age group and gender should be kept unredacted/visible, given high-level nature of this information.
- Agency is responsible to ensure highest quality and integrity of information collected in EudraVigilance [Reg Art 24(3)].
  - NCAs and MAHs should implement audit systems for quality control, compliance monitoring and duplicate detection of ICSRs before reporting them.
  - Regular control by Agency of quality, integrity & compliance for all organisations submitting ICSRs to EudraVigilance.

GVP Module VI: Main aspects

Reporting modalities: Interim arrangements

Applicable to solicited/unsolicited valid ICSRs (healthcare/non-healthcare).

a. Serious ICSRs: 15 days time frame

- MAHs shall report all serious ICSRs occurring in EU to NCA on whose territory suspected adverse reactions occurred;
- MAHs shall report all serious ICSRs occurring outside EU, including those received from competent authorities to
  - EudraVigilance database, and
  - NCAs of Member States where medicinal product is authorised, if required.
- NCAs shall ensure that all serious ICSRs occurring in their territory and that are reported to them, including those received from MAHs, are made available to EudraVigilance database.
- NCAs should also make available, to MAHs of the suspected medicinal products, all serious ICSRs reported directly to them.

b. Non-Serious ICSRs: 90 days time frame

- If required, MAHs shall report all non-serious ICSRs occurring in EU to NCA on whose territory suspected adverse reactions occurred.

GVP Module VI: Main aspects

Reporting modalities: Final arrangements

Once the functionalities of the EudraVigilance database specified in [Reg Art 24(2)] are established.

Applicable to solicited/unsolicited valid ICSRs (healthcare/non-healthcare).

a. Serious ICSRs: 15 days time frame

- MAHs shall submit all serious ICSRs that occur within or outside EU, including those received from competent authorities outside EU, to EudraVigilance database only.
- NCAs shall submit all serious ICSRs that occur in their territory and that are reported directly to them to EudraVigilance database.

b. Non-Serious ICSRs: 90 days time frame

- MAHs shall submit all non-serious ICSRs that occur in EU to EudraVigilance database only.
- NCAs shall submit all non-serious ICSRs that occur in their territory to EudraVigilance database.

GVP Module VI: Conclusions

1. GVP VI summarises all legal requirements and guidelines applicable to NCAs, MAHs and the Agency
   - Collection, data management and reporting of unsolicited/ solicited cases of suspected adverse reactions
     - Associated with medicinal products for human use authorised in EU, independently of their condition of use and
     - Reported by healthcare professionals, patients or consumers.
2. MAHs should have systems in place
   - For collection, recording and management of all relevant information on cases of suspected adverse reactions reported to them;
   - Structured in way that allows for reports of suspected adverse reactions to be validated in timely manner and reported to NCAs/ Agency within legal expedited time frame (including as well those reports received by contractual partners or organisations belonging to same group of companies).

GVP Module VI: Conclusions

3. Only valid ICSRs of suspected adverse reactions should be reported
   - 4 minimum criteria need to be present,
   - Electronically by all stakeholders,
   - Based on internationally agreed formats, standards & terminologies and highest data quality.
4. Audit systems implemented by stakeholders for quality control, compliance monitoring and duplicate detection of ICSRs. Regular control performed by Agency on all organisations submitting ICSRs to EudraVigilance.

Thank you

Questions?

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