EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Good Vigilance Practice Module VI

Management and reporting of adverse reactions to medicinal products

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Signal Detection and Data Analysis
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GVP Module VI: Scope

GVP VI addresses the legal requirements detailed in Title IX of Directive 2001/83/EC and Chapter 3 of Regulation (EC) No 726/2004.

GVP VI summarises legal requirements and guidelines applicable to competent authorities in Member States (NCAs), Marketing Authorisation Holders (MAHs) and the Agency as regards the 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.

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.
- Highlights distinctions with safety reporting rules applicable to clinical trials conducted in accordance with Clinical Trials Directive 2001/20/EC.
- Requirements specific to NCAs in order to encourage reporting from healthcare professionals, patients and consumers.
- Requirements specific to MAHs in relation to medicinal products for which they hold ownership within or outside EU, including those applicable to same group of companies or when having concluded commercial 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,
  - 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

- NCAs and MAHs should take all appropriate measures in order to collect and collate all reports of suspected adverse reactions to medicinal products originating from unsolicited or solicited sources.
- 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.
- Only valid cases of suspected reactions qualify for expedited reporting: Reporter(s), only 1 patient, suspected medicinal product(s), reaction(s).
  - Reasonable possibility of causal relationship between a suspected medicinal product and a noxious or unintended response, which arises from the medicinal product independently of its condition of use by a patient [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 considered by reporter or sender.

GVP Module VI: Main aspects

Collection and Reporting: Provisions applicable to MAHs

- MAHs record all reports of suspected adverse reactions (EU/non-EU) occurring in post-authorisation studies [Dir. Art 107(1)]: Solicited reports derived from 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: Provisions applicable to MAHs (Contd.)

- For non-interventional studies
  - Report only valid ICSRs occurring in non-interventional studies with primary data collection directly from patients or healthcare professionals, where possible relationship between an event and a suspected medicinal product considered by reporter or MAH.
  - For non-interventional study designs based on secondary use of data, 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: Provisions applicable to MAHs (Contd.)

- MAHs shall only submit ICSRs published in scientific and medical literature for those journals and active substances not monitored by Agency. Until lists are published, MAHs 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;
  - Literature articles based on analysis from NCAs databases in EU;
  - Literature articles presenting summary data analysis from publicly available databases or detailing patients in tables or line listings.
- Events/observations which are not valid ICSRs but which may affect risk-benefit balance of medicinal product
  - 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.
- 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

GVP VI summarises all legal requirements and guidelines applicable to NCAs, MAHs and the Agency as regards the collection, data management and reporting of unsolicited/solicited cases of suspected adverse reactions associated with medicinal products for human use authorised in EU reported by healthcare professionals, patients or consumers.

NCAs and 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.

Only valid ICSRs should be reported electronically by stakeholders based on highest internationally recognised data quality standards.

Audit systems implemented by NCAs and MAHs for quality control, compliance monitoring and duplicate detection of ICSRs.

Thank you

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