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Guideline on Specific Adverse Reaction Follow-up questionnaires (Specific AR FUQ)

Draft

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Guideline on Specific Adverse Reaction Follow-up questionnaires (Specific AR FUQ)

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Executive summary

This paper aims at providing a guidance to the EU/EEA regulatory medicines network on when and how to use specific adverse reaction follow-up questionnaires (Specific AR FUQs) in routine pharmacovigilance activities.

The completeness of information in Individual Case Safety Reports (ICSRs) is essential in many pharmacovigilance assessments. However, the information available in these reports is often limited and may lack essential data that would allow for better characterisation of the reported adverse reactions. To address this issue, forms and questionnaires are commonly used to collect additional information when initial reports are incomplete. These include general follow-up questionnaires (FUQ) and Specific AR FUQs.

This paper provides guidance on the use of Specific AR FUQs and focuses on Specific AR FUQs developed by the MAHs at the request of NCAs and does not intend to modify the MAHs internal policies for FUQs. It emphasizes the importance of obtaining structured and detailed information on reported adverse reactions that may impact the benefit-risk balance of a product or have implications for public health.

The document identifies three main directions: providing general guidance on when and how to use Specific AR FUQs, guidance for MAHs on developing Specific AR FUQs, and considering discontinuation and removal of Specific AR FUQs.

The guidance outlines the requirements for a Specific AR FUQ and recommends that a Specific AR FUQ should be used for safety concerns that may impact the benefit-risk balance of a product. For important identified risks listed in the product information, FUQs should not be generally used, but in some special situations, a Specific AR FUQ may be necessary for further characterization of the risk.

The content of a Specific AR FUQ should focus on collecting the missing data of main importance for assessing the safety concerns in question and should be prefilled with available information to avoid requesting the primary source to repeat information. A Specific AR FUQ should not be extensive and its completion by the reporter should be easy to minimize the burden on reporters and to avoid discouraging future spontaneous reporting.

The format and dissemination of Specific AR FUQs should follow existing recommendations to optimize data collection. This includes having a common structure and contain a preface, basic content, and specific content with questions addressing essential aspects of the adverse reaction. The MAHs are not expected to use Specific AR FUQ for case reports that are not initially and directly sent to them (e.g., cases reported to NCAs or other MAHs).

To facilitate knowledge sharing, a tool is being developed to list and publish approved Specific AR FUQs.

Overall, in addition to existing GVP guidelines, this guidance provides a framework for the use and implementation of Specific AR FUQs as part of risk management in routine pharmacovigilance activities to improve the completeness of information in pharmacovigilance.

1. Introduction (background)

The completeness of information in Individual Case Safety Reports (ICSRs) is essential in pharmacovigilance assessments. However, the information available in the ICSRs is sometimes limited and may not always provide important information that would allow to better characterise the adverse reaction (AR) reported.

Forms and questionnaires are used to collect additional information as part of routine pharmacovigilance when information in initial reports is incomplete. These include general follow-up questionnaires (e.g., for pregnancy exposure to medicinal products) or companies' internal check lists that are used to collect more data on spontaneous reports or Specific Adverse Reaction Follow-up questionnaires (Specific AR FUQs) which aim to obtain standardised, structured, and detailed information from the reporter on a particular AR.

For general FUQs, the existing guidelines and the requirements from the GVP Module VI apply, e.g., for pregnancy FUQ, EMA's guideline on the exposure to medicinal products during pregnancy[1] or for medication errors[2].

2. Scope

To facilitate completeness of initial information, Specific AR FUQ refers to FUQs that are deemed necessary to obtain structured and detailed information on reported adverse reactions (ARs) that may have an impact on the benefit risk balance of the product or have implications for public health.

The scope of this guidance is limited to specific (or targeted) AR FUQs requested by the competent authorities. It does not intend to modify or change the MAHs' internal policy for FUQs.

The MAH is not expected to collect further information about a case report that is not initially and directly sent to them (e.g., cases reported to NCAs or other MAHs)[3].

Three main directions have been identified for the present document:

- Providing general guidance (when and how to use Specific AR FUQs) to competent authorities in Member States (NCAs), Pharmacovigilance risk assessment committee (PRAC), pharmacovigilance and clinical assessors, pharmacovigilance (GVP) inspectors, Marketing authorisation holders (MAHs) and the European Medicines Agency (EMA), using the opportunity of ongoing EMA work on updates of GVP guidelines
- Developing guidance that can be used by MAHs and recommend if and how approved Specific AR FUQs could be published
- Considerations on discontinuation and removal of Specific AR FUQs

3. Legal basis

This guideline should be read in conjunction with all relevant information included in current and future EU guidelines based on the Directive 2001/83/EC [DIR] and Regulation (EC) No 726/2004 [REG], and ICH guidelines and regulations, especially:

- Guideline on good pharmacovigilance practices (GVP) Module V – Risk management systems
- Guideline on good pharmacovigilance practices (GVP) Module VI – Collection, management, and submission of reports of suspected adverse reactions to medicinal products
- Guideline on good pharmacovigilance practices (GVP) Module VII – Periodic safety update report

[1] https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/guideline-exposure-medicinal-products-during-pregnancy-need-post-authorisation-data_en.pdf
[2] https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/good-practice-guide-recording-coding-reporting-assessment-medication-errors_en.pdf
[3] https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/guideline-good-pharmacovigilance-practices-gvp-module-vi-collection-management-submission-reports_en.pdf

- Guideline on good pharmacovigilance practices (GVP) Module IX – Signal management
- Guideline on good pharmacovigilance practices (GVP) Annex I - Definitions
- Guideline on the exposure to medicinal products during pregnancy: need for post-authorisation data – EMEA/CHMP/313666/2005
- Good practice guide on recording, coding, reporting and assessment of medication errors - EMA/762563/2014

4. Guidance on the use of the Specific AR FUQ

4.1. Requirements for a Specific AR FUQ

Adverse reactions for which Specific AR FUQs are considered can be defined as those referring to safety concerns[4] (from RMP and/or PSUR) for which the collection of information as detailed as possible and their better characterisation may have an impact on the B/R balance of the medicinal product.

For medicinal products requiring a Specific AR FUQ but without an RMP in place (exceptional and/or for old products), the Specific AR FUQ could be associated to a safety concern identified and/or followed-up in the PSUR.

If there is a RMP already in place, the (new) Specific AR FUQ referring to the relevant safety concern should be included into the RMP (annex 4).

As Specific AR FUQs are related to safety concerns which could impact the benefit/risk balance of a medicinal product, the number of situations requiring such questionnaires is expected to be limited. For important identified risks which are listed in the product information as undesirable effects (section 4.8 of the SmPC) and for which a frequency has been determined above 1/1000[5], Specific AR FUQs should in principle not be used because the burden for Healthcare Professionals would be significant. However, in some special situations, where the reversibility, severity or other aspects of the important identified risk need to be further characterised, a Specific AR FUQ might be necessary.

When assessing whether a Specific AR FUQ should be recommended, consideration should be given to other tools in place which collect more data on the same risk (e.g., PASS) and to what extent a Specific AR FUQ would be of additional value.

Specific AR FUQs are considered as routine pharmacovigilance.

Specific AR FUQs used by different applicants/MAHs (including for generics) for the same adverse reaction should be kept as similar as possible. MAHs are strongly encouraged to share the content of their questionnaire(s) upon request from other MAHs.[6]

4.2. Content of the Specific AR FUQ: aspects to be considered

Specific AR FUQs should focus on the collection of missing data of particular importance which were not initially provided by the reporter.

The Specific AR FUQ should be prefilled by the MAH with all the available information collected at the time of the initial report, to limit the burden on the reporters.

[4] Important identified risk, important potential risk and missing information
[5] i.e. very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100)
[6] https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-good-pharmacovigilance-practices-module-v-risk-management-systems-rev-2_en.pdf

Additional questions should be strictly limited to the collection of standardised information and detailed information on a particular adverse reaction to better characterise a safety concern.

In line with GVP Module VI, the length of the Specific AR FUQ should be as short as possible.

This guidance proposes a common structure of Specific AR FUQ which should be used and adapted to fit within existing MAH and NCA practices. These Specific AR FUQs should contain three parts:

- A preface to explain the added value of this Specific AR FUQ (to increase the willingness of reporters to complete the Specific AR FUQ and thus provide relevant additional information) e.g., *"You have reported an adverse reaction(s) of XXXX for "medicinal product name". This questionnaire is being sent to you for obtaining valuable additional information about the reported case to thoroughly evaluate the relation to "medicinal product name" exposure. The questionnaire is already prefilled with all the available information collected at the time of the initial report, only additional information should be filled in. By providing as detailed information as possible, you can make a useful contribution to the safety of "medicinal product name"*.
- A basic content (such as the patient age, gender, dates of drug intake, date of adverse reaction occurrence / resolution, outcome, medical history, concomitant medications).
- A specific content with questions covering essential aspects to be considered (i.e., detailed data on the adverse reaction) to allow the characterisation of an adverse reaction and/or assessment of the causality between the adverse reaction and the medicinal product. The aspects to be considered should be identified when the need for this Specific AR FUQ emerges and should display the minimum content of information usually lacking but nevertheless essential to perform a causality assessment and a better characterisation of the adverse reaction. They could address the following points (but not limited to):
  - Context of use (including the exact therapeutic indication),
  - Risk factors related to the specific adverse reaction,
  - Clinical/biological data including specific laboratory values (reference values should be asked for where relevant), histopathological results, imaging data, or any other relevant data (e.g., autopsy investigations in case of fatal outcome), that enable either the confirmation of the adverse reaction or exclusion of other causes.

Regarding the approval of the content of the Specific AR FUQ, it is worth noting that the GVP Module V on the format of the risk management plan (RMP) in the EU provides the following guidance for Specific AR FUQs: *"should be described in the routine pharmacovigilance activities section and copies of these forms should be provided in RMP annex 4"*. (see GVP Module V, Section V.B.6.1.1) Therefore, Specific AR FUQs within an RMP usually require a review of the exact content by the competent authorities. However, the depth of review may differ depending on e.g., the type of procedure or pharmacological considerations and may be limited to a consistency check.

Caution should be applied when choosing the name of the Specific AR FUQ, to fit with MedDRA terms and to avoid terms at SOC level or vague medical concepts that could be considered too broad to characterise a safety concern.

4.3. Format of the Specific AR FUQ

In general, the format, content and layout of the Specific AR FUQ should follow recommendations from GVP Module V and GVP Module VI to optimise collection of the missing information. Specific AR FUQs should use:

- Tick boxes where possible, to save time of the reporter.

- At least one free text field to enable responders to provide any additional information.

It is the responsibility of the MAHs to ensure that submitted Specific AR FUQs are readable and understandable by the responders with a content as short as possible. The review of the Specific AR FUQ could involve panel experts in the field of the (physio-)pathology and adverse reaction of interest.

Specific AR FUQs should be sent by the MAHs to the reporters in the local language of the reporter. The translations in local languages are the responsibility of the MAHs.

4.4 Dissemination of the Specific AR FUQ

The dissemination of Specific AR FUQ to Reporters is performed by the MAHs for suspected adverse reactions reports received directly to them.

The tools used for the dissemination can include different means like emails, web-based questionnaires, apps, phone, mail, fax, and letters. Reminders should always be included, and their timing should be defined[7].

5. Publishing of Specific AR FUQ

To share the existing Specific AR FUQs in place, a tool is being developed by the EMA to list and publish (annex 4 and/or full RMP) Specific AR FUQs approved by competent authorities and covered (*link to the tool when available)* by the scope of this guidance.

To simplify the collection and search of existing Specific AR FUQ, the heading of the Specific AR FUQ should be titled with the name of the medicinal product and the MedDRA term best reflecting the underlying safety concern.

6. Considerations on discontinuation and removal of Specific AR FUQ

Characterisation of risks through use of Specific AR FUQ might become necessary at any time throughout the lifespan of a medicinal product and should be discontinued when the safety concern has been sufficiently characterised.

The MAHs should ensure that the Specific AR FUQs are implemented in an effective and timely manner.

The MAHs are encouraged to regularly assess the effectiveness of the Specific AR FUQs, using process and outcome indicators:

- **Process indicators** (e.g., a response rate) can be used to monitor whether the targeted recipients (to be detailed by the MAHs) of the Specific AR FUQs respond to the request for more information. While process indicators cannot provide evidence on whether a Specific AR FUQ is effective, a low response rate should trigger further analysis. For instance, a low response rate could be related to the questionnaires not reaching the target (i.e., the reporter of the adverse reaction), the request not being identified as important by the target, an inadequate format or collection means, a lack of readability, or complex response process.
- **Outcome indicators** (e.g., details about the specific information collected after the implementation of the specific AR FUQ). Competent authorities may request to the MAHs to provide a detailed analysis of the additional information provided and to substantiate how it contributes both to increase the quality of the data collected when compared with the initial information and to

[7] GVP VI.B.7.1. (Submission time frames of ICSRs)

a better characterisation of the safety concern with a potential impact on the benefit/risk balance of the medicine. The outcome indicators should reflect the added value of the information collected compared to what already existed in the initial ICSR.

Effectiveness results should be submitted upon request of the competent authorities in a procedural framework (e.g., PSUR, RMP update).

Discontinuation and removal of a Specific AR FUQ in light of the characterisation of the safety concerns over time can be considered when a Specific AR FUQ is assessed as successful, for example led to reclassification of an important potential risk as an important identified risk or a as a non- important risk (i.e. that would not warrant to be followed up through a safety concern in the RMP) or led to the conclusion that there is no causal association based on the additional information reported and the important potential risk can be removed from the RMP and/or PSUR.

Definitions and abbreviations

Specific Adverse Reaction Follow-up questionnaires (Specific AR FUQs): Questionnaires which aim is to obtain standardised, structured, and detailed information on reported suspected adverse reactions of special interest and go beyond general follow-up questionnaires.

B/R – Benefit/Risk

ADR reporting – Adverse drug reaction reporting

AR – Adverse reaction (synonyms: Adverse drug reaction (ADR), Suspected adverse (drug) reaction, Adverse effect, Undesirable effect)

EMA – European Medicines Agency

FUQ – Follow-up questionnaire

GVP – Good pharmacovigilance practices

HCP – Healthcare professional

ICSR – Individual case safety report

MAH – Marketing authorisation holder

MedDRA – Medical Dictionary for Regulatory Activities

NCA - National competent authority

PASS – Post-authorisation safety study

PRAC – Pharmacovigilance risk assessment committee

PSUR – Periodic safety update report

RM – Risk management

RMP – Risk management plan

SmPC – Summary of product characteristics

SOC – System organ class

Specific AR FUQ – Specific adverse reaction follow-up questionnaire

References

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