PHV-3 version 3 Non-Interventional Post-Authorisation Safety Studies of Medicinal Products for Human Use

This guideline replaces PHV-3 guideline version 2 effective from 4 February 2014.

The guideline provides a detailed description of terms, governs the conditions for performing the studies, provision of information and documents to the State Institute for Drug Control (SÚKL) in the area of non-interventional post-authorisation safety studies (PASS) of medicinal products for human use that are conducted in the Czech Republic and are initiated, managed or financed by a marketing authorisation holder voluntarily or pursuant to obligations imposed under Art.31a or 32a of Act No. 378/2007 Coll., on Pharmaceuticals, as amended (hereinafter referred to as "AoP") or under Art. 21a or 22a of Directive 2001/83/EC (hereinafter referred to as "Dir.").

The rights and obligations imposed on the marketing authorisation holder by the Act on Pharmaceuticals shall not be affected by this guideline.

This guideline should help distinguish non-interventional PASS from clinical trials, other types of studies and marketing activities of marketing authorisation holders. It also lays down a procedure for notifying the SÚKL about non-interventional PASS to strengthen and increase the efficiency of pharmacovigilance practices.

Non-interventional PASS are one of the tools of active pharmacovigilance for obtaining valid data and conducting of reasonable PASS presents a significant benefit for the evaluation of the safety profile of medicinal products under the conditions of common practice.

Types of non-interventional safety studies:

A non-interventional PASS can be performed:

a) Voluntarily by the marketing authorisation holder
b) Based on an obligation imposed by a regulatory authority (SÚKL, EMA, other national authorities of the Member States) as a part of the initial marketing authorisation application (AoP Art.31a, Dir. Art.21a)
c) Based on an obligation imposed by a regulatory authority (SÚKL, EMA, other NAs) due to an emerging safety concern – during a post-authorisation phase (AoP Article 32a, Dir. Art.22a)

Related Regulations:

- Act No. 378/2007 Coll., on Pharmaceuticals as amended (hereinafter referred to as the "AoP")
- Decree No. 228/2008 Coll., on Registration of Medicinal Products, as amended (hereinafter referred to as the "Decree")
- Directive 2001/83/EC (as amended by Directive 2010/84/EU)
- Guideline on Good pharmacovigilance practices (GVP) – Module VIII – Post-authorisation safety studies
- Commission Implementing Regulation No. 520/2012

Affected clauses of AoP:

§ 93j, 93k of the Act

§ 3a of the Act

§ 17a of the Decree

Abbreviations:

Non-interventional PASS	Non-interventional post-authorisation safety studies
GVP	Guideline on Good vigilance practices
EMA	European Medicines Agency
PRAC	Pharmacovigilance Risk Assessment Committee
SmPC	Summary of Product Characteristics
RMP	Risk Management Plan for a medicinal product
PSUR	Periodic Safety Update Report
NA	National Authority
EU PAS	European Register of Post-Authorisation Studies
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
AoP	Act No. 378/2007 Coll., on Pharmaceuticals as amended

1. Definitions

*Post-authorisation safety study (*Article *3a (1) of AoP)*

Post-authorisation safety study of a medicinal product for human use shall mean any study relating to an authorised medicinal product for human use conducted with the aim of identifying, characterising or quantifying a safety hazard, confirming the safety profile of the medicinal product, or of measuring the effectiveness of risk management measures.

*Non-interventional post-authorisation study (*Article *3a (2) of AoP)*

Non-interventional post-authorisation safety study of a medicinal product for human use shall mean any study in which an authorised medicinal product for human use is prescribed in the usual manner in accordance with the terms of the marketing authorisation and in which the assignment of the patient to a particular therapeutic strategy is not decided in advance by a study protocol but falls within current practice and the prescription of the medicine by the attending physician is clearly separated from the decision to include the patient in the study, while no additional diagnostic or monitoring procedures are applied to the patients and epidemiological methods are used for the analysis of collected data; non-interventional post-authorisation studies include epidemiological, pharmaco-economic and research studies.

Non-interventional post-authorization safety study

It is a subset of post-authorisation safety studies covered by this guideline. The term "non-interventional post-authorisation safety study" is reserved only for a study that meets all the following conditions:

1. The study is conducted with the aim of identifying, characterising or quantifying a safety hazard, confirming the safety profile of the medicinal product, or of measuring the effectiveness of risk management measures.
2. The studies shall not be performed where the act of conducting the study promotes the use of a medicinal product.
3. Payments to healthcare professionals for participating in non-interventional post-authorisation safety studies shall be restricted to the compensation for time and expenses incurred.
4. Only authorised medicinal products in accordance with the terms of the marketing authorisation are used in the study.

5. Medicinal products in the study are used in accordance with the current effective SmPC. Any changes to the SmPC or other regulatory actions regarding the safe use of the products must be immediately taken into consideration in the performed studies.
6. Medicinal products used in the study have to be already marketed in the Czech Republic and available in the usual distribution network.
7. Medicinal products in the study are prescribed and dispensed in the usual way, i.e. prescribed by a physician and dispensed by a pharmacist based on a prescription. No promotional samples can be used.
8. Medicinal products in the study shall not be provided for free or at discount compared to their current availability in the market. This also applies to the additional payments in pharmacy.
9. The selection of patients assigned in the study shall not be affected in advance and must depend solely on the decision of the attending physician as a part of the current practice. The participating physician should comply with the approved protocol of the study and the approved SmPC during the study.
10. No additional diagnostic or monitoring procedures shall be applied to the patients and epidemiological methods are used for the analysis of collected data. All diagnostic and therapeutic procedures that are applied to the patients included in the study shall be reimbursed in the usual manner, i.e. without any support from the organizer of the study. Some exceptions are situations where diagnostic procedures recommended in the SmPC are not sufficiently performed in current practice and these procedures are necessary for drug safety monitoring.

Studies that do not meet all 10 conditions may not be described as "non-interventional post-authorisation safety studies". In case that MAH submits the documentation to a study that cannot be described as non-interventional safety study, SÚKL will inform the MAH that it is necessary to change the type of study to a marketing study, PAES (post-authorisation efficacy study), other type of the study or a clinical trial.

In a study, which is described as a retrospective study, only such data may be used, that have been recorded on data media (including paper) before the first contact between the organizer of the study, or its representative, and the physician.

Study protocol (research plan)

All PASS must have a written study protocol before the study commences. The study should follow a scientifically sound study protocol developed by individuals with appropriate scientific background and experience. Strongly recommended and appropriate format and content of the protocol are provided in the document titled *Guidance for the format and content of the protocol of non-interventional post-authorisation safety studies* *(http://www.ema.europa.eu/docs/en_GB/document_library/Other/2012/10/WC500133174.pdf)*.

- Basic information that shall be included in each PASS protocol (according to Annex III of the Commission Implementing Regulation No. 520/2012):
  - Title page (informative title including a commonly used term indicating the study design and the medicinal product substance or drug class concerned, subtitle with a version identifier and dates of the last version)
  - Marketing authorisation holder
  - Responsible parties (author of the protocol, collaborating physicians and investigators, list of collaborating institutions and other relevant study sites)
  - Abstract - stand-alone summary of the study protocol
  - Amendments and updates to the study protocol
  - Milestones and timetable of the study stating the following milestones: start of data collection,

end of data collection, final study report
- Rationale and background
- Research question and objectives
- Research methods
- Protection of human subjects
- Management and reporting of adverse reactions/ events
- Plan for disseminating and communicating study results
- References

The format and content are obligatory for the imposed studies and strongly recommended for studies performed voluntarily by the marketing authorisation holder.

SÚKL will publish protocol abstracts of studies conducted in the Czech Republic. In case that the study is conducted also in other Member States, it is possible to submit the protocol in English; otherwise the protocol is presented in Czech. The abstract of the protocol must be always submitted also in Czech.

- Recommended format of the abstract (according to Annex III of the Commission Implementing Regulation No. 520/2012):
  - Title with subtitles including version and date of the protocol, name and affiliation of main author
  - Rationale and background
  - Research question and objectives
  - Study design
  - Subjects and study size, setting
  - Variables
  - Data sources
  - Discussion
  - Milestones

Progress reports

A progress report may be requested by SÚKL at any time during the study conduct, particularly in situations requiring information regarding safety concern arising from the study.

Final study report

The marketing authorisation holder shall submit the final study report to SÚKL within 12 months of the end of data collection. If the study has not been conducted or was discontinued, the MAH shall submit a document replacing the final study report and provide the reasons for termination of the study. Strongly recommended and appropriate format and content of the final study report are provided in the document titled *Guidance for the format and content of the final study report of non-interventional post-authorisation safety studies (http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2013/01/WC500137939.pdf).*

- Basic information that shall be included in each PASS final study report (according to Annex III of the Commission Implementing Regulation No. 520/2012):
  - Title page (informative title including a commonly used term indicating the study design and the medicinal product substance or drug class concerned,, subtitles with date of final report and name and affiliation of the main author)
  - Abstract - stand-alone summary of the final study report

- Marketing authorisation holder and investigators (names, titles, degrees, addresses and affiliations of the principal investigator and all co-investigators and list of collaborating institutions and relevant study sites)
- Milestones and timetable of the study (planned and actual dates)
- Rationale and background Research question and objectives
- Amendments and updates to the protocol
- Research methods
- Results
- Discussion and conclusion
- References

The format and content are obligatory for the imposed studies and strongly recommended for studies performed voluntarily by the marketing authorisation holder.

If the results of the study are used for a scientific publication, it is recommended to familiarize SÚKL with the final manuscript of the paper.

SÚKL will publish abstracts of the final study reports of the studies conducted in the Czech Republic. In case that the study is conducted also in other Member States, it is possible to submit the final study report in English; otherwise the final study report is presented in Czech. The abstract of the final study report must be always submitted also in Czech.

Recommended format of the abstract of the final study report (according to Annex III of the Commission Implementing Regulation No. 520/2012):

- Title, with subtitles including date of the abstract and name and affiliation of main author
- Keywords (not more than five keywords indicating the main study characteristics)
- Rationale and background
- Research question and objectives
- Study design
- Setting
- Subjects and study size, including dropouts
- Variables and data sources
- Results
- Discussion (including, where relevant, an evaluation of the impact of study results on the risk-benefit balance of the product)
- Marketing authorisation holder
- Names and affiliations of the principal investigators

2. How to notify SÚKL/EMA of performing PASS

A) How to notify SÚKL of studies performed voluntarily by the MAH (type a)

The extent of information and method of notifying SÚKL of performing voluntary PASS is based on legal requirements – see related regulations. The MAH is obliged to notify SÚKL electronically of an intention to conduct PASS **at least 60 days before commencement of the study** while providing the following information:

- Company name (MAH/CRO) or name of the organization performing the study, address
- Identification of the product in the study, SÚKL code that is assigned to the product
- Title of the study

- Identification number of the study according to MAH´s documents
- Date of start of data collection, expected date of end of data collection, expected date of end of data analysis and expected date of the final study report submission
- Study protocol

The MAH is obliged to notify SÚKL electronically of the completion of a non-interventional post-authorisation safety study. The marketing authorisation holder shall submit the final study report to SÚKL within 12 months of the end of data collection.

The marketing authorisation holder shall use the appropriate interactive form available on the SÚKL website to inform SÚKL about the start/end of the study.
http://www.sukl.eu/modules/nps/index.php?lang=2

The marketing authorisation holder shall evaluate whether the study results have an impact on the marketing authorisation. If necessary, the MAH shall submit an application to vary the marketing authorisation - within 12 months of the end of data collection together with the final study report. The MAH shall monitor the data generated while the study is being conducted and consider their implications for the benefit/risk balance of the medicinal product concerned.

All non-interventional PASS shall be described in the Risk Management Plan for a medicinal product (RMP) in accordance with GVP Module V-RMP. All relevant sections/modules of the RMP should be amended to document the conduct of the study, including the safety specification, the pharmacovigilance plan, the risk minimisation plan and the summary of activities, as appropriate. A copy of the study protocol approved by the competent authority should be provided in annex 6 of the RMP. When a RMP does not exist, a new RMP should be developed referring to the PASS.

The results of all non-interventional PASS (even negative results) shall be provided in the PSUR (Periodic Safety Update Report) in the relevant section (III-8 "Findings from non-interventional studies"). A list of non-interventional studies in the relevant period (see GVP Module VII) shall be annexed to the PSUR.

B) How to notify SÚKL of studies requested by a regulatory authority (type b and c)

The marketing authorisation holder conducting a non-interventional post-authorisation safety study based on the conditions and obligations imposed under Article 31a or 32a AoP only in the Czech Republic, shall submit a draft protocol to SÚKL **at least 60 days before its commencement**.

If the study is conducted in multiple Member States, the marketing authorisation holder shall submit the draft protocol to the Pharmacovigilance Risk Assessment Committee (PRAC) and to the Agency.

Within 60 days from the submission of the draft protocol, SÚKL issues one of the following:

a) a letter endorsing the draft protocol ;

b) a letter of objection that shall set out in detail the grounds for the objection in any of the following cases:

- it is considered that the conduct of the study promotes the use of a medicinal product;
- it is considered that the design of the study does not fulfil the study objectives; or

c) a letter notifying the MAH that the study is a clinical trial falling under the scope of Directive 2001/20/EC.

The study may commence only when the written endorsement from SÚKL or the PRAC, as appropriate, has been issued. When a letter of endorsement has been issued by the PRAC, the marketing

authorisation holder shall forward the protocol to SÚKL and may thereafter commence the study according to the endorsed protocol.

After the protocol is endorsed by the relevant authority, the MAH shall electronically notify SÚKL about the commencement of the study by providing the following information:

- Company name (MAH/CRO) or name of the organization performing the study, address
- Identification of the product in the study, SÚKL code that is assigned to the product
- Title of the study
- Identification number of the study according to MAH´s documents
- Date of start of data collection, expected date of end of data collection, expected date of end of data analysis and expected date of the final study report submission
- Approved study protocol

The MAH is obliged to notify SÚKL electronically of the completion of a non-interventional post-authorisation safety study. The marketing authorisation holder shall submit the final study report to SÚKL within 12 months of the end of data collection.

The marketing authorisation holder shall use the appropriate interactive form available on the SÚKL website to inform SÚKL about the start/end of the study.

http://www.sukl.eu/modules/nps/index.php?lang=2

The marketing authorisation holder shall evaluate whether the study results have an impact on the marketing authorisation. If necessary, the MAH shall submit an application to vary the marketing authorisation - within 12 months of the end of data collection together with the final study report. The MAH shall monitor the data generated while the study is being conducted and consider their implications for the benefit/risk balance of the medicinal product concerned.

All non-interventional PASS shall be described in the Risk Management Plan for a medicinal product (RMP) in accordance with GVP Module V-RMP. All relevant sections/modules of the RMP should be amended to document the conduct of the study, including the safety specification, the pharmacovigilance plan, the risk minimisation plan and the summary of activities, as appropriate. A copy of the study protocol approved by the competent authority should be provided in annex 6 of the RMP. When a RMP does not exist, a new RMP should be developed referring to the PASS.

The results of all non-interventional PASS (even negative results) shall be provided in the PSUR (Periodic Safety Update Report) in the relevant section (III-8 "Findings from non-interventional studies").A list of non-interventional studies in the relevant period (see GVP Module VII) shall be annexed to the PSUR.

C) How to notify EMA of performing a non-interventional PASS (type a, b c)

According to GVP, in order to support transparency, it is strictly recommended to notify EMA on all safety studies conducted by the marketing authorisation holder (non-interventional PASS conducted voluntarily or pursuant an obligation). The marketing authorisation holder should make study information available in the EU electronic register of post-authorisation studies (EU PAS Register) maintained by the Agency and accessible through the European medicines web-portal. The study protocol should be entered in the register before the start of data collection. The EU PAS Register is publicly available.

So far, EU PAS can be found here: http://www.encepp.eu/encepp/studiesDatabase.jsp

SÚKL recommends MAHs to enter study information regarding all conducted studies in the EU PAS Register.

3. Notification forms to inform SÚKL

A) Non-interventional post-authorisation study initial notification form

Information on the medicinal product

SÚKL code (identification of the product)

Enter the SÚKL code in format 702 or 0000702.

Based on the entered code, additional identification information about the medicinal product and the marketing authorisation holder are automatically loaded into the form.

If the study is conducted with multiple medicinal products, the form allows an addition of multiple SÚKL codes.

Information on the study

Type of study - select one of the options. In case that the study is imposed by the regulatory authority, tick the appropriate box in the form.

As the next step, enter the study title, identification number of the study according to MAH´s documents, objectives of the study (up to 500 characters) and further characteristics of the study (choose from the options).

Dates

Enter the date of the start of data collection, expected date of the end of data collection, expected date of the end of data analysis and expected date of the final study report submission of in the dd.mm.yyyy format.

*"Start of data collection" is the date from which information about the first study subject is first recorded in the study dataset, or, in the case of the secondary use of data, the date from which data extraction starts;

* "End of data collection" is the date from which the analytical dataset is completely available.

Study protocol

For studies conducted voluntarily by the MAH: Insert the study protocol.

For studies imposed by a regulatory authority: Insert the approved version of the study protocol and the date of approval of the study protocol.

Attach other documents related to the study (e.g. questionnaire).

Enter Information on person responsible for the study who will be the contact point for SÚKL.

After completing the form, insert the electronic signature to submit the form. **Please note that only Czech electronic signature may be used to submit the notification**. After electronic signature, "Confirmation of receipt of data regarding a non-interventional post-authorisation study" will display on the new page. The confirmation provides basic information regarding your notification and an **SÚKL identification number** allocated to the study **and a password** are generated. Your study will be registered in the SÚKL PASS registry under this number. Make sure you save the information from the notification for a future reference (to fill-in the edit form/end-of-study notification form).

B) Non-interventional post-authorisation study edit form

If necessary, some of the entered information about the study may be changed/amended/clarified. Fields which may be changed are: Data and Comment.

To use the edit form, it is essential to have the SÚKL identification number of the study and the password.

C) Non-interventional post-authorisation study end-of-study notification form

The MAH is obliged to notify SÚKL electronically of the completion of a non-interventional post-authorisation safety study. The marketing authorisation holder shall submit the final study report to SÚKL **within 12 months of the end of data collection**. **It is not possible to fill-in end-of-study form without submitting the final study report.**

To use the end-of-study form, it is essential to have the SÚKL identification number of the study and the password.

Date

Enter the date of the end of data collection (according to the final study report) and the date of the final study report submission.

Final Study Report - *required field*

Insert the final study report (pdf or doc format).

The field "Form of payment and site costs" is optional for safety studies (intended for marketing studies).

Enter Information on person responsible for the study who will be the contact point for SÚKL.

After completing the end-of study form and submitting the form with the electronic signature, the notification is completed.

4. Documents for audit and inspection

The marketing authorisation holder shall ensure the fulfilment of its pharmacovigilance obligations in relation to the study and that this can be audited, inspected and verified.

The marketing authorisation holder shall have the following clearly identifiable documents regarding the PASS available while the study is being conducted and at least for the period legally required:

a) documents that provide a detailed description of the research methods and objectives of the study, including data collection and evaluation (research plan, setting , etc.), contact information on study sites and investigators.

b) documents containing data obtained from the study (e.g. questionnaires, adverse event reports, etc.).

c) documentation on analytical dataset, study results, statistical programmes used for generating data.

d) interim reports and final study reports.

e) materials used in the study - e.g. educational materials.

f) publications that use the findings of the study (final manuscript).

In some cases also other documents may be requested:

g) study budget with a detailed cost breakdown to individual parts of the study, especially site specific payments.
h) contracts/agreements between individual parties involved in the study.

5. Recommended sources of further information

While PASS is being planned and conducted, it is recommended by SÚKL to follow the principles of Good vigilance practices (GVP) Module VIII as well as principles of Good epidemiological practices issued by epidemiology and pharmacoepidemiology societies and scientific bodies. These principles can be found here:

- http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000345.jsp&mid=WC0b01ac058058f32c#section5 (GVP)
- http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2012:159:0005:0025:EN:PDF (Commission Implementing Regulation No.520/2012)
- http://www.encepp.eu/standards_and_guidances/index.shtml
- http://www.pharmacoepi.org/
- http://www.epiresearch.org/index.php
- http://www.cioms.ch/
- STROBE statement: http://www.strobe-statement.org/index.php?id=available-checklists
- PRISMA statement: http://www.prisma-statement.org/statement.htm