Directive 2010/84/EU

**Article 21a added**

(...) a marketing authorisation for a medicinal product may be granted subject to one or more of the following conditions:

(b) to conduct post-authorisation safety studies;

The marketing authorisation shall lay down deadline for the fulfilment of these conditions as necessary.
 Directive 2010/84/EU, Art. 22a

Regulation (EU) No 1235/2010, Art. 10a

After the granting of a marketing authorisation, the national competent authority may impose an obligation on the marketing authorisation holder:

(a) to conduct a post-authorisation safety study if there are concerns about the risks of an authorised medicinal product (...);

The imposition of such an obligation shall be duly justified, notified in writing, and shall include the objectives and timeframe for submission and conduct of the study.
Directive 2010/84/EU, **Art. 107m**

1. This Chapter [*Supervision of post-authorisation safety studies*] applies to non-interventional post-authorisation safety studies which are initiated, managed or financed by the marketing authorisation holder voluntarily or pursuant to obligations imposed in accordance with Articles 21a or 22a, and which involve the collection of safety data from patients or healthcare professionals.

2. This Chapter is without prejudice to national and Union requirements for ensuring the well-being and rights of participants in non-interventional post-authorisation safety studies.

Directive 2010/84/EU, **Art. 107n to 107q**

Only for studies conducted as an obligation
Procedures for study protocol and final report submission and approval
Implementing Measures in order to harmonise the performance of pharmacovigilance activities provided for in Directive 2001/83/EC and Regulation (EC) No 726/2004

Annex IV applies to non-interventional post-authorisation safety studies initiated, managed or financed by a marketing authorisation holder under obligations imposed by a national competent authority, the Agency or the Commission in accordance with Articles 21a and 22a of Directive 2001/83/EC and Articles 10 and 10a of Regulation (EC) No 726/2004.

→ Protocols, abstracts and final study reports for post-authorisation safety studies
Post-authorisation safety study: definition

Any study relating to an authorised medicinal product 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.
Objectives of a PASS may include:

- to characterise the safety profile of a medicine
- to provide reassurance about the absence of a safety concern related to a specific adverse reaction
- to investigate potential or identified risks
- to evaluate risks of a medicinal product used in authorised indications by patient groups not studied in the pre-authorisation phase
- to assess patterns of drug utilisation and use of the medicinal product that may have an impact on its safety
- to evaluate the effectiveness of a risk minimisation activity
PASS may be initiated, managed or financed by a MAH:

• Voluntarily

• Pursuant to an obligation imposed by a competent authority
  ➢ as a condition to the granting of the marketing authorisation, or
  ➢ after the granting of a marketing authorisation if there are concerns about the risks of the authorised medicinal product

Obligation is a condition to the marketing authorisation.

Obligation duly justified based on benefit-risk considerations.

Close supervision (protocol, progress reports, final report)
Post-authorisation safety study

- Clinical trial
- Non-interventional study

The MAH has the responsibility to ensure that the PASS is not a clinical trial.

If the PASS is a clinical trial, Directive 2001/20/EC and Volume 10 of The Rules Governing Medicinal Products in the European Union shall apply.

GVP Module VIII mainly applies to non-interventional trials.
General guidance and requirements in Good Pharmacovigilance Practice

Guiding principles:

• Scientific standards
• Transparency
• Harmonisation
• Quality control

Applies to all PASS

Level of enforcement depends on the type of studies and topic
General guidance and requirements

General principles

- Consideration to relevant scientific guidance (e.g., ISPE, ENCePP)
- Investigators qualified by education, training, and experience
- Research contract
  - Compliance to regulatory requirements
  - Investigator’s scientific expertise to be exercised
  - ENCePP Code of Conduct recommended
General guidance and requirements

**Study protocols**

- Transmission to relevant competent authorities
- Involvement of QPPV
- Registration into EU public registry of PASS
- Change control
  - substantial amendments
General guidance and requirements

Reporting of pharmacovigilance data

• data relevant to the risk benefit balance

• expedited reporting of serious ADRs
  • for studies with secondary use of data
    → no requirement for expedited reporting; events/reactions summarised in final study report
  • for studies with primary use of data
    → expedited reporting where possible relationship between an event and a suspected medicinal product considered by reporter or MAH
General guidance and requirements

**Study reports**

- Progress reports
  - may be requested before study commences or any time during study conduct – timing to be agreed
- Final study report
  - to be submitted as soon as possible after finalisation within 12 months
  - transmission to competent authorities
- Publication of results by investigators
- Submission of published study results
General guidance and requirements

Format and content of study protocols and study reports

- Described in Implementing measures and GVP
- Obligation for studies imposed as an obligation
- Recommendation for studies conducted voluntarily
- Technical contribution from EMA to European Commission
- Based on international guidance, e.g.
  - ISPE
  - STROBE, CONSORT
  - ENCePP Checklist for Study Protocols
  - ENCePP Guide for standards in pharmacoepidemiology
General guidance and requirements

Registration of studies in EU registry of non-interventional post-authorization safety studies (« ENCePP » registry)

- Recommended for all post-authorisation safety studies
- Transparency
- Tool for obligation to EMA to publish study protocols and final results of imposed PASS concerning Centrally-authorised products
- Tool for communication and exchange of information
- Minimisation of administrative procedures and duplication of work.
General guidance and requirements

Quality systems, audit and inspections

• Fulfilment of obligations in relation to study can be audited, inspected and verified.

• Traceability and documentation of any change to data.

• Analytical dataset and statistical programme used to generate results to be kept in electronic format and available for auditing and inspection

• MAH should ensure that external investigators are qualified by education training or experience to perform their tasks.
General guidance and requirements

Data protection

- MAH should ensure that all study information is handled and stored in such a way that it can be accurately reported, interpreted and verified, while the confidentiality of the study subjects remains protected.

- Directive 95/46/EC on the protection of individuals with regard to the processing of personal data and on the free movement of such data.

- Relevant legislation and guidance of Member States where the study is conducted.
Thank you!