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# Role of the Post-Marketing Authorisation Studies in Drug Risk Surveillance: Specifications and Methodologies

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**Abstract –** Studies conducted after the marketing authorisation with the objective of identification, characterization or quantification of one or more risks (called PASS "Post-Authorisation Safety Studies"), have been strengthened in the past years with the implementation of the concept of risk management plans (RMPs), established in 2005 in the European regulatory framework and recently amended as part of the community revision.

These safety studies, interventional or not, are related to a marketed drug, whether or not the drug is used within the market authorisation conditions. Apart from these safety studies, other studies whose primary objective is not risk assessment, including assessment of efficacy, description of prescription data and use in real life, pharmacokinetics, public health impact . . . can complete available safety data.The Giens Round Table examined PASS from the risk management plans of a sample of marketing authorisation holders (participants to the Round Table) and identified the main characteristics of proposed actions. Concerning the specifications and the choice of methodology, only a general outline has been sketched in view of the complexity and diversity of drug risks situations.

## 1. Introduction

Since 2005 in Europe, the marketing authorisation (MA) holders have to submit a risk management plan for the majority of drugs, as part of the European marketing authorisation dossier, following detailed guidelines[1] and a specific model.[2] This proactive drug risk management system is based on all clinical and non clinical available data and it contains pharmacovigilance actions, including additional safety studies and risk minimisation measures, when needed.[3,4] If the post-marketing safety studies are an important tool in this system, fundamental questions remain. One question that arises in particular is whether the choice criteria for study methodology could be summarized in specifications based on the type of risks and/or scientific objective (identification or quantification of certain adverse effects, assessment of the impact of measures to minimize risks . . .).

## 2. Regulatory framework

Safety studies, interventional or not, have as a common criterion to target a marketed drug used theoretically within the MA conditions. This definition and its practical implementation have quickly raised regulatory concerns because conducting an observational study only within the approved indications does not always reflect the "real life". It took until the new community legislation to have this issue addressed.

⋆ For the list of participants, see end of article

### 2.1. Community revision

The 2001/83/EC Directive amended by the 2004/27/EC Directive and 2004/726/EC Regulation were revised as part of the pharmaceutical package by the 1235/2010 Directive and 2010/84/EU Regulation adopted in December 15, 2010 and published in the Official Journal of the European Union of December 31, 2010,[5,6] which means an implementation of the Regulation from 12 July 2012 and for the Directive a transposition into national law no later than July 21, 2012.

#### *2.1.1. Main provisions, outside the post-MA studies*

Among the new features of the Directive, it can be noted in relation to routine Pharmacovigilance a broader definition of adverse reaction, the possibility for the patients to report adverse effects, an enhanced signal detection, changes in the modalities of preparation and submission of periodic safety update reports (PSUR) and clarification of procedures for the evaluation of pharmacovigilance data. An important element is the creation of a new committee more independent and autonomous, with expanded responsibilities, called PRAC for “pharmacovigilance risk assessment committee”, which will replace the European Pharmacovigilance Working Party (PhWG). The mandate of the PRAC shall cover all the aspects of the drug risk management. Moreover, provisions on communication and transparency have been integrated, including a drug list with enhanced surveillance, the development of a European web-portal with a link to national portals, the possibility of public hearings and access to spontaneous reports included in the Pharmacovigilance database EudraVigilance.

#### *2.1.2. Post-authorisation safety studies*

Section 1 of the Directive introduces a broader definition of PASS: any study, interventional or not, with 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. The payments to healthcare professionals involved in these studies shall be restricted to compensation of time and expenses incurred.

More detailed provisions were introduced on the validation and monitoring of the protocols of the studies initiated, managed or funded by the marketing authorisation holder, with a significant coordination and evaluation role of the PRAC (or national authority in the case of a study performed in only one Member State). Regulatory actions based on the results of these studies could be taken quickly. It is also intended to give public access to the summary of results. Finally, it is important to underline the introduction of post-authorisation efficacy studies (PAES), which can be requested where questions relating to some aspects of the efficacy of the product are identified and can only be answered after the product is marketed or because of scientific or methodological progress.

### 2.2. Future national provisions

At the national level, a parliamentary bill on research involving Humans, called "Jardé’s law" will be further discussed by the members of the parliament.[7] It covers research organised and carried out on humans for the development of biological or medical knowledge. This bill is primarily intended to introduce a regulatory framework for non-interventional studies, which are characterized by the fact that all acts are performed and products used in the usual way, without additional or unusual procedures of diagnosis, treatment or monitoring. The most significant measures would be to request a positive opinion of the committee for the protection of persons (CPP) prior to the implementation of these studies, to assign new missions to the CPP replacing those of the advisory committee on the treatment of information on research in the field of health (CCTIRS), to register those studies and their results in a public directory within a reasonable timeframe. It will be necessary to be cautious to the introduction of these new measures, which should be aligned as much as possible with the provisions of the revised community regulation. Otherwise France would be less attractive than other European countries for the conduct of safety observational studies, in particular by increasing the duration of these studies, already approved by the new European PRAC.

### 2.3. The other studies

Apart from the safety studies conducted after approval, it should not be disregarded that other studies may complement the available safety data, although their main objective is not the risk assessment but efficacy in the context of a new indication for example, description of drug prescription or use and the therapeutic strategy under real conditions, pharmacokinetics or pharmacodynamics, physiopathology, evaluation of the impact on public health through different types of study requested by the Transparency Commission and/or the Evaluation Committee for Health Products, and also market studies.

### 2.4. The ENCePP network

The European network of centres for pharmacoepidemiology & pharmacovigilance (ENCePP) is a European network initiated

by the European Medicines Agency, intended to further strengthen the post-marketing surveillance of the health care products by facilitating the conduct of multicenter studies, focusing on the risk assessment or risk / benefit ratio. This network includes nearly 80 institutions/units in the field of Pharmacovigilance and Pharmacoepidemiology which are composed of research and medical-care centers, healthcare databases, electronic registries or registries dedicated to rare diseases or adverse effects. Since 2007, this network has worked to establish a checklist of methodological standards [8] and to adopt a code of conduct [9] to promote transparency and independence of research conducted within the network.

The checklist of the methodological standards was developed primarily with a view to improving the quality of studies, encouraging investigators to meet some important epidemiological principles. The code of conduct covers aspects such as the development of the study protocol, the conduct of the study, data ownership and access to data and publication of the results. People who want to conduct an ENCePP study must commit to a high level of transparency, including publication of the study results whether negative or positive, and making public relevant information on the protocol before the study starts. In order to facilitate compliance with these rules, the European Medicines Agency (EMA) is currently developing an electronic register which will be an accessible tool to the public, for the registration and consultation of Pharmacoepidemiology and Pharmacovigilance studies conducted in Europe. Moreover, in June 2010 the European Medicines Agency and the ENCePP officially launched the " ENCePP studies" which will be awarded by a scientific committee to Pharmacoepidemiology studies meeting ENCePP standards. [10]

## 3. Current situation: analysis of the risk management plans

### 3.1. Methods

Firstly, a literature review was performed on two topics: the use, impact or methodology of the PASS, and the risk management plans. The articles dealing specifically with the databases used to perform PASS or related to PASS examples were not retained.

In parallel, a survey was conducted among marketing authorisation holders participating in the roundtable discussions to identify and characterize the PASS proposed in the European RMP or requested by the French health authorities. In practice, a table was sent to the firms asking them to fill in, for each product, the risks described in the RMP (important identified risk, important potential risk, missing information), and the PASS designs. For each PASS, it was asked to specify if French patients were enrolled and the existing databases used, where appropriate.

Finally, members of the Round Table suggested a synthesis of the indications on each type of study depending on the objective, on the nature of the risk, but also on different criteria (frequency of the event, of the exposure, etc.).

### 3.2. Literature review

Different types of actions can be proposed for pharmacovigilance, from spontaneous reporting to Post-Authorization Safety Studies. Their relevance was analyzed in the context of the evaluation of the risk/benefit ratio of marketed drugs. [11–13] The different methodologies used for PASS are discussed, from proactive surveillance to comparative studies, as well as criteria of choice. These include:

- Proactive pharmacovigilance and data from registries. In the case of registries, data are systematically collected on consecutive patients and followed at long term.
- Descriptive epidemiological studies
- Analytic epidemiological studies: they include case-control studies, cohort studies and studies derived (case crossover study ...). The retrospective cohort studies and case-control studies are facilitated by access to existing data collected in a systematic and reliable way, such as databases like general practice database (GRPD) in the United Kingdom or PHARMO in the Netherlands.
- Clinical trials (or clinical trials extensions) specifically designed to identify or quantify one or more risk(s) related to a product, which has been granted marketing authorisation.

Risks and commitments in terms of pharmacovigilance actions are included in the RMP submitted at the same time as the MA dossier. Frau *et al*. described the European RMP of 15 drugs approved by the committee for medicinal products for human use (CHMP) through a centralised procedure, between 2006 and 2007: [14] the type of risk (identified risk, potential risk, missing information) was specified only for 7 drugs, PASS were provided for 13 products (the total number of PASS was not specified). Similarly, Giezen *et al*. described European RMP of 18 drugs approved by the CHMP between November 2005 and May 2007: [11] 96% of the studies had a safety objective and 11% were drug utilisation studies (some studies with a mixed objective), 75 % were cohort studies and 23% were clinical trials (including extensions of clinical trials), 41% of the studies were conducted by academics and 46% were made from data registries.

Since 1998, the scientific contribution of PASS has drawn the attention of Hasford *et al*. [12] They examined 35 observational

post MA studies in the areas of hypertension, psychiatry, rheumatology and analgesia, identified from publications or by contacting the marketing authorisation holders. Safety was an endpoint for 31 of these studies; no study included a comparison group. Out of the 21 studies providing information about the eligibility criteria, 17 presented highly selective criteria, similar to those of clinical trials, thus not sufficient to assess the risk in real conditions of use. The median follow-up was relatively short and not relevant to the risk occurring away from the exposure.

The availability and completeness of PASS protocols at the time of RMP submission to the health authorities have been analyzed by Giezen *et al.*:[11] 26% of PASS had a limited protocol, i.e. with 11 to 15 of 17 items recommended by the International society for pharmacoepidemiology (ISPE)[15] and 74% of the PASS offered only a synopsis (between 6 and 10 items) or a brief description (1 to 5 items), not allowing to assess the relevance and feasibility of the proposed studies. The authors concluded that protocols should be validated by health authorities with possible discussions between applicants and Competent Authorities before submission.

Frau *et al.*[14] investigated to what extent the planned studies were ultimately carried out, based on a search of their publications and their status in the study registries such as "clinicaltrials.gov" or the World health organization (WHO) registry in using the identifier mentioned in the RMP status: out of the 13 drugs for which a PASS was proposed, 5 studies were in progress two years after marketing. Similarly, Harmark *et al.* found that proposed studies are rarely put in place.[3]

The role of RMP in improving risk management is discussed by Frau *et al.* ;[14] among the 15 drugs, 12 have safety issues after marketing, resulting in a total of 39 type II major variations to the summary of product characteristics (SPC): a single modification was related to a risk confirmed by a PASS planned in the RMP; 19 variations were associated to risks not described in the RMP, 13 variations resulted from a risk confirmed by a PASS not provided with the RMP and 6 variations resulted from periodic safety update reports (PSUR) as part of routine pharmacovigilance. In addition, the authors identified 9 communication measures on product safety for 6 of these 12 drugs. They conclude that RMP are poorly predictive of actual risks occurring after marketing, that the planned pharmacovigilance actions are insufficiently followed in practice (PASS not conducted) and that communication on SPC modifications is not sufficient.

### 3.3. Survey on PASS carried out by a sample of marketing authorisation holders through the European RMP Framework

Among the products marketed by 6 pharmaceutical companies, 33 molecules with EU-RMP have been collected, including 8 in the field of oncology, 6 biotherapeutics and 3 vaccines. The average number of risks listed in the RMP was 4.6 (1 to 15 according to the molecules). The types of risks are distributed as follows:

- Fivety seven potential risks including mainly specific adverse effects (n=50) and risk of misuse (n=5)
- Fourty five missing information concerning primarily populations not included in clinical trials (n=38) and co-administration with other molecules (n=6)
- Fourty one identified risks including essentially specific adverse effects

One hundred and seventy-nine PASS were assessed with an objective of identification, characterization and quantification of these risks. These studies were mostly defined as clinical trials (n=76 including 10 studies defined as extensions of clinical trials). There are also studies with additional safety analysis performed on data from ongoing (n=11) or finalized (n=11) trials, comparative observational studies (n=31) including a majority of cohort studies (n=24), non-comparative observational studies (n=18), mainly prospective (n=16), active surveillance (n=25, including 15 from registries), one meta-analysis and 6 with a non specified design. Only 29% of these studies included French patients of which only one was a comparative observational study.

This inventory shows a variability of the types of studies proposed as part of RMP: clinical trials remain a large majority, 76% of studies are comparative, very few are case-control or case-crossover studies and very few are drug utilization studies. The studies are usually conducted to meet targeted objectives, and we identify a limited number of studies aimed in detecting new risks.

Clinical trials are much more initiated in the case of missing information instead of confirming a potential or identified risk; the latter being more the subject of supplementary analysis performed from existing trials. Comparative observational studies are both suggested in the case of missing information related to an unassessed exposure (co-administration for example) or to confirm a risk. Active surveillance and drug utilization studies (descriptive studies) are mainly proposed to detect a misuse.

The interpretation of these data must take into account the fact that they come from a particular sample not necessarily representative of all RMP. In addition, analysis of these RMP has highlighted the confusion raised by the terminology used to define the types of studies. Thus, the term "cohort" is used indifferently to describe a comparative study evaluating a risk by comparing the incidence of adverse events in patients exposed to the drug to the patients not exposed to the drug, or a non-comparative study estimating this incidence only in patients exposed to the drug; in the latter case, the lack of reference group does not allow to characterize the additional drug-related risk. Similarly, the wording

"registry" does not permit to know precisely the type of study based on registry data. Moreover, it is often wrongly attributed to the term "registry" to cohort studies, which are not exhaustive. Finally, the term "clinical trial" was used indifferently for clinical trials and extensions of trials, the latter being related to the monitoring of patients all exposed to the drug and therefore not including in a control arm (so it is rather a cohort study without unexposed group and with strict eligibility criteria for these patients were initially included in a clinical trial).

Finally the French agency for safety of health products (Afssaps) may ask marketing authorisation holders to ensure that French centers will be integrated in the studies requested by the EMA under the European RMP. In addition, the French Agency may assess the relevance of conducting national studies, according to specific French situations.

When additional studies are planned, it is mainly drug utilisation studies in order to characterize the profile of prescribers and patients, to know the real conditions of use, to define the risk of pharmacodependence, to identify abuse and off-label use. "Before and after" studies also allow to measure the impact of a SPC change or any other measure of risk minimization. In general, they provide with utilisation data in France.

## 4. Indications of different study types

Depending on the specifications of the risks described in the RMP at the time of application for marketing authorisation, certain types of studies are more suitable than others to assess these risks in the post-marketing setting/context. As a reminder, the different types of risk are:

- **Important identified risk**: safety issue that might have an impact on the balance of benefits and risks of the medicinal product, for which there is adequate evidence of a causal relationship with the drug
- **Important potential risk**: safety issue that may impact on the risk / benefit ratio for which the association with the drug is mentioned, but must be confirmed
- **Important missing information**: the information is not available at the time of application for marketing authorization (special populations, potential co-administration with another product. . .)

The different study designs discussed during the roundtable are summarised in table I.

## 5. Conclusion

In our case study, it appears that the post-authorisation safety studies conducted to date within the framework of European Risk Management Plans are mostly clinical trials (or clinical trials extensions), to a lesser extent observational studies, and for less than a third include French patients.

Current situation shows heterogeneity in the terminology used to qualify study types. Significant effort should be undertaken to standardize their denomination. Apart from European RMP's PASS, post-MA studies can be requested by the national Health Authorities; they are primarily drug utilization and public health impact studies with safety data. Furthermore, even if difficult in some situations (uncertain drug place in therapeutic strategy . . .), PASS protocols should be validated by Health Authorities when requesting market authorisation.

Participants in the Giens Round Table underlined that there was no simple solution for the choice of the study method, and such choice should take into consideration the following parameters: target population, exposure (frequency, product access conditions, indications and contraindications, place in the treatment strategy), risk (frequency and nature, baseline risk in the target population, latency, identification of potential risk at the time of marketing or afterwards). The decision must be based on the level of evidence provided by the contemplated studies but also on feasibility parameters.

If detailed specifications for practical realisation and methodological options were not developed due to the complexity and the diversity of drug risk situations, a draft of an initial outline was issued. Several studies and designs are sometimes necessary to address one safety concern.

Every situation is specific, therefore it is imperative to use a pharmacoepidemiological expertise.

## Participants

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**Table I.** Indications, advantages and limitations of the different study designs in pharmacoepidemiology.

| Study design | **Indication** | **Advantages** | **Limitations** |
|---|---|---|---|
| Spontaneous reporting | • Unknown risk and low baseline rates<br>• Signal generation | • System well implemented<br>• Reimbursed and non-reimbursed products<br>• Regulatory required | • Under-reporting<br>• Uncertain denominator<br>• Not effective in case of high baseline rates<br>• Not appropriate for long latency and not identified risks |
| Active surveillance<br>Ex : *Prescription Event Monitoring* | • Estimation of AE incidence rates<br>• AE frequency moderate to high<br>• Well established product in the market | • Limitation of under-reporting<br>• Allows to calculate incidence rates, fast<br>• Poorly expensive | • Product must be well established in the market<br>• Information collected from a sample of the source population<br>• Selection bias for physicians and patients<br>• Measurement bias |
| Cross-sectional study | • Characterisation of the treated population<br>• Identification of "off label usage" | • Easy to perform, fast<br>• Relatively inexpensive | • Does not allow to quantify the risk<br>• Does not take into account the risk temporality |
| Non comparative prospective cohort study | • Estimation of AE incidence rates in "real life"<br>• Identification of sub-groups at higher risk | • Can be rapidly performed just after the marketing authorisation<br>• Representative of the population being treated<br>• Comprehensiveness of collected data | • Selection bias for physicians and patients<br>• Indirect comparaisons: important biases<br>• Relatively expensive<br>• Not appropriate for uncommon or long latency AE<br>• Losts to follow-up |
| Case-control /<br>Case-crossover study | • Evaluation of an additional risk<br>• All risks, including rare AE<br>• Exposure must be sufficiently frequent | • Allows to assess multiple exposures<br>• Less expensive and faster than a cohort study | • Selection of control subjects: must have the same probability as the cases to be exposed to the drug<br>• Validity of the exposure information (recall bias, difficult in case of long latency outcome)<br>• Allows to assess only one AE |
| Prospective comparative cohort study (exposed / non exposed) | • Evaluation of an additional risk<br>• AE frequency moderate to high, whatever the baseline rate<br>• Allows to assess rare exposures | • Comprehensiveness of outcomes<br>• Representative of the population being treated<br>• Unbiased exposure measure<br>• Allows comparative risk quantification<br>• Allows to assess multiple AE | • Difficulty in the selection of the comparator(s)<br>• "Depletion of susceptible" bias (if prevalent users), confounders (adjustment), indication bias<br>• Not effective for rare AE<br>• Long to complete and expensive<br>• Losts to follow-up<br>• Allows to assess only one exposure |

**Table II.** Continued.

| Study design | Indication | Advantages | Limitations |
|---|---|---|---|
| Study using data from medical or reimbursement database (cohort or case-control study) | • See comparative cohorts and case-control studies<br>• Quantification of an additional risk, including rare risks (for a prescribed product for a medical DB and for a reimbursed product for a reimbursement DB)<br>• Product well established in the marketplace | • Rapid to perform<br>• Poorly expensive<br>• Fewer selection bias and no measurement bias<br>• Allows the comparison between therapeutic classes<br>• Powerful | • Only the data available in the DB, limiting the possibilities of adjusting<br>• Difficulty to estimate the biases<br>• Limited access<br>• Quality concerns / missing data<br>• Multiplicity of tests |
| Safety randomised trial | • Quantification of an additional risk, comparatively to a reference treatment<br>• AE frequency moderate to high | • Groups comparability (randomisation); minimises the biases (particularly if double blinded).<br>• Effective if high baseline rate | • Not representative of the population being treated<br>• Long to complete, expensive<br>• Ethical concerns: difficult to obtain authorisation from ethical committees and adhesion from investigators if risk already identified |
| Safety meta-analysis | • Quantification of an additional risk, comparatively to a reference treatment<br>• AE frequency moderate to high, whatever the baseline rate | • Powerful (high number of patients),<br>• Minimises the biases<br>• Not expensive (more in case of individual data)<br>• Identification of sub-groups at higher risk if individual data<br>• Effective if high baseline rate | • Aggregation of randomised controlled trials data (heterogeneity: eligibility criteria, doses and/or duration of treatment, modalities of data collection).<br>• Lower quality of safety data, individual data required to aggregate the diagnostic codes<br>• Results can be discordant according to the studies included<br>• Representative of the population included in the trials |

**AE**: adverse event; **DB**: database

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