

Opportunities and Challenges of Pan European Post-Marketing Surveillance Programmes



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Almost 40 years ago LJ Witts wrote “the final test of the safety of a drug is in fact its release for general use” (1). The last report of the Committee on Safety of Drugs (which became the Committee on Safety of Medicines) noted that “no drug which is pharmacologically effective is without hazard. Furthermore, not all hazards can be known before a drug is marketed”. These comments highlight that patients must then, despite the regulatory controls, expect to experience unknown reactions when new drugs are launched onto the market. This realisation has defined the purpose of what has become known as post-marketing surveillance (PMS). PMS represents a constant vigilance to identify as yet unknown adverse drug reactions, in the smallest possible exposed populations, and includes a number of methods.

WHY DO WE NEED TO CONTINUOUSLY EXPAND OUR KNOWLEDGE ON A PRODUCT'S SAFETY PROFILE?

Highly standardised, placebo-controlled, multicentre, randomised clinical trials are considered the gold standard for assessing the efficacy of new medicines. However, for a number of valid reasons, the full safety profile of a drug is rarely identified in such trials. Some key limitations in most Phase II / III trials have been highlighted by Stricker & Psaty (2):

- ◆ Selective populations – the inclusion and often extensive exclusion criteria of most trials mean that by the time of registration the drug has been tested in a highly targeted population and almost certainly not in the elderly, children or pregnant women.
- ◆ Duration – most Phase III trials occur over a short duration (maximum six months) even for chronic treatments. This, together with often only a 30 day follow-up post final dose, precludes the discovery of long-term consequences of a drug.
- ◆ Number – even in the most extensively trialled drugs, the product is likely to have been administered to less than 10,000 and frequently fewer than 5,000 people. These numbers significantly reduce the chance of identifying rare but potentially important adverse events. In fact, it has been shown that the median number of patients forming the safety database of newly licensed medicines involving new active substances is only 1,528 (95 per cent confidence intervals 1,194-1,748) subjects (3).
- ◆ Artificial situation – due to the fact that clinical trials aim at achieving a high internal validity, they

are often well removed from ‘real life’ clinical practice, for example limited co-medications are allowed, patients have restricted co-morbidities and compliance is closely monitored.

POST-MARKETING SURVEILLANCE

Once a drug has been launched, there are a number of methods by which adverse drug reactions can be further evaluated, identified and monitored. These include: spontaneous reporting (for example the UK’s yellow card scheme); observational safety studies often sponsored by the market authorisation holder (MAH); prescription event monitoring (PEM), as undertaken by the Drug Safety Research Unit at the University of Southampton; and follow-up via large computerised databases such as the General Practice Research Database (GPRD).

Company sponsored observational PMS studies are often viewed with some scepticism as they are seen as ‘seeding’/ marketing trials for the company to promote new drugs. However, when properly conducted they have an important role to play in further understanding the safety of these drugs. To further enhance the quality of data collected, some PMS studies incorporate quality assurance procedures such as randomised auditing or central monitoring.

To provide greater direction and increase the scientific credibility of company sponsored PMS studies, guidelines and regulations have been developed both at a European and national level. European and local specific guidance available from three specific countries in Northern Europe is described below.

PMS studies may be hypothesis generating (those studies conducted for the purpose of identifying previously unrecognised safety issues); hypothesis-testing in order to

substantiate a causal association (investigating possible hazards); and confirming safety profile (verify the expected safety profile of a medicinal product under marketed conditions). They may also be conducted to quantify established adverse reactions and identify risk factors.

PMS studies are non-interventional, observational programmes that ‘look over the doctor’s shoulder’ and consider the drug in normal clinical practice. In this format, the studies are considered to be outside the scope of the EU Directive and therefore ICH-GCP does not have to be fully adhered to – an important consideration for sponsors when undertaking a programme where large numbers of patients are to be enrolled. Non-interventional studies are defined within the EU Directive as those trials where the product is prescribed in the usual manner, in accordance with the SPC, with the decision to enrol a patient being clearly separated from the physician’s decision to prescribe medication and without additional interventions or clinic visits beyond current practice (EU Directive 2001). Country guidelines along with the Post Authorisation Safety Study (PASS) guidance obviously highlight the need for a rigorous scientific objective and the absence of any influence over the physicians prescribing behaviour. The population studied should be as representative as possible of the general population of users, with exclusion criteria being limited to the contraindications given in the SPC. To reflect real life practice in a broad population and to avoid any potential financial inducement, it is expected that the protocol stipulates the minimum and maximum number of patients to be entered by a single doctor. The medicinal product(s) should be prescribed in the usual manner (for example in the UK using a FP10). It is only once the decision to prescribe has been taken that a patient can be asked to participate in the PMS programme and both the choice of therapy prescribed and identification of patients for inclusion are completely at the physician’s discretion.

Table 1: Similarities and Differences for Conducting PMS studies in Three European Countries

	UK	Germany	The Netherlands
Guidelines	SAMM	BfArM recommendations no guidelines	CGR
Ethic requirements	Yes MREC, LREC (in some cases) and local hospital / health authority	Generally no, but observational studies have the potential for a number of conflicts of interest can arise (for example data protection) where ethic committee input can be helpful*	Not mandated but can be submitted to one EC to confirm study is non WMO bound and therefore CGR code applies
Informed consent	Required (written)	Not required	Not required (written) Required (verbal)
Insurance	No	No	Depending on procedures
Company involvement from sales force	Must be clearly separated from a promotional call	Involvement permitted	Must be clearly separated from a promotional call
Physician payments	Clear guidelines (BMA fee schedule)	For efforts which go beyond standard care, in line with the medical fee ordinance (ärztliche Gebührenordnung)	In line with fees in the Health Care Act and relevant professional organisations
Regulatory approval	Yes	No, but notification to BfArM and National Association of Statutory Health Insurance Physicians	Not if sponsor SOP in place for protocol development
Drug supply	By prescription	By prescription	By prescription

* Can be referred to relevant professional codes and laws and especially to the different legislations applicable to physicians in the individual German Federal States

Observational cohort studies should normally include appropriate comparator group(s). The comparator group(s) will usually include patients with the disease/indication(s) relevant to the primary study product and such patients will usually be treated with alternative therapies.

European guidance is provided by the Post Authorisation Study (PAS) guidelines, which are applicable to any study conducted within the SPC and under normal conditions of use. A subsection of these guidelines are the PASS, which specifically considers safety studies (vol 9 pharmacovigilance). PASS are defined as those studies which are:

- ◆ Within the terms of the marketing authorisation
- ◆ Have the objective of identifying or quantifying as a safety hazard
- ◆ When the number of patients in the study will add significantly to the existing data on the product
- ◆ When the drug is either provided by the marketing authorisation holder (MAH) or prescribed in the normal way either in general practice or in the hospital setting

In the UK, the Safety Assessment Marketed Medicines (SAMM) guidelines have existed since 1994 (MCA 1994) and are applicable to all company-sponsored studies which evaluate the safety of marketed products. These were developed by a working group comprised of the Medicines Control Agency (now Medicines and Healthcare Products Regulatory Agency), Committee on the Safety of Medicines (CSM), the Association of the British Pharmaceutical Industry (ABPI), British Medical Association (BMA) and the Royal College of General Practitioners (RCGP).

In the Netherlands, studies are only defined as observational if: the medicinal product is investigated in normal medical practice; participants are not subjected to treatment or required to behave in a certain manner; tests/procedures do not deviate from normal standards; and there is no randomisation to treatment. When all of these conditions are met, the Stichting Code Geneesmiddelenreclame (CGR) Code of Conduct for Pharmaceutical Advertising, with special reference to Article 16, is applied.

For PMS studies undertaken in Germany, the recommendations for the planning and implementation of observational studies from the BfArM (Bundesinstitut für Arzneimittel und Medizinprodukte/Federal Institute for Drugs and Medical Devices) should be followed. Observational studies are defined there as follows – observational studies are intended to gather findings in the use of marketable medicinal products. Their special feature is that they do not influence the physician in charge of the treatment in his diagnosis or choice and implementation of therapy for the individual case. The aim is to observe therapeutic measures under the condition of routine use

of a medical product by physician and patient. Observational studies can be designed without a control group, for example product-oriented, or with two or more control groups, for example indication-oriented. They are conducted with commercial products. Further details of individual country requirements are given in Table 1 (see page 107).

WHO, WHERE AND HOW MANY?

The scientific credibility of PMS studies, especially when MAH sponsored, are sometimes questioned. To overcome this issue and potentially assist with regulatory and ethical negotiations, independent steering committees (or advisory boards) comprised of experts in the therapeutic area can be convened to ensure the protocol and results are sufficiently robust to withstand peer review.

Even though pharmaceutical company-sponsored PMS programmes have tended to be run on an individual country basis, there is a strong rationale for utilising multinational programmes. Drug safety is applicable in all countries where a drug is marketed and the increased number of patients adds to the robustness of any findings producing data (and publications) that are more readily available to participating physicians in all countries, compared to country-specific regulatory agency reports. Under normal, spontaneous adverse event reporting, there can be substantial differences in the number of reports to regulatory authorities in each country. An example of this is bupropion, marketed in Canada (Wellbutrin and Zyban) and in the UK (Zyban), despite the product being available in Canada longer and with two indications that the number of reported events is significantly different – twice as many adverse drug reactions (ADRs), 11 times more deaths and 3.8 times more seizures per 1,000 prescriptions have been reported in the UK than Canada (3). Multinational programmes do require more effort internally within the sponsor, as both consistency and flexibility are required to develop core materials, for example protocol and CRFs. A core data set (minimally the primary and key secondary endpoints) must be identified and consistency maintained by all countries to allow for integrated data analyses and comparisons to be made across geographies. Flexibility to meet local regulations or address clinical interests might include the addition of secondary endpoints generating data on specific sub-groups and adding local value to the individual country results and reports.

The group of physicians invited to participate in a PMS programme are primarily dictated by where the drug under consideration is mostly prescribed (primary or secondary care), taking into account the patient pathway for ongoing care. As PMS studies are designed to be ‘real life’ clinical practice, participating physicians, particularly general practitioners in some countries (for example Italy and the UK), are likely to be research naïve. It is therefore important that participation in the programme is made as easy as possible, with consideration

given to maximising simplicity and minimising processes outside of normal practice. Ongoing, easy and rapid access to assistance provided either by the sponsor or their nominated delegate (for example a contract research organisation) to answer questions from sites is important. This, together with appropriate training on the study (and if needed the product), can assist in smoother execution.

Within the realms of practicality, the more the better is the norm when it comes to both participating physicians and recruited patients. To reliably identify any adverse event that occurs in more than one in 1,000 patients, at least 10,000 patients need to be enrolled. Most PMS studies collect data on between 500 and 30,000 patients. In Germany, where PMS studies are considered an integral part of launching a new drug, some 'mega studies' are undertaken when patient enrolment is in excess of 50,000.

BENEFITS OF PARTICIPATING IN A PMS STUDY

Primarily, by enrolling into a large scale PMS study, subjects are helping to provide further data on the safety profile of a new medicine. Given the observational nature of PMS studies, enrolment in a given study will not impact a patient's care. The altruistic appeal of participating in medical research is to improve the understanding of care and management of the disease the participant has. Some studies also allow the patient to provide feedback regarding their view of the new therapy, for example ease of use and satisfaction with the new treatment regime or changes in their quality of life.

By participating in PMS programmes, physicians may become aware of relevant and important safety information more quickly than they would through national regulatory summaries, study updates and final programme publications as a result of the under-reporting of spontaneous ADRs noted above. Involvement can also facilitate physicians' own understanding of a new treatment and provides an opportunity to participate in scientific discussions with peers and leaders in a given speciality. Having potential international, national and local findings also provides physicians with access to and the potential to share local data.

BENEFITS TO PHARMACEUTICAL COMPANIES

When MAH sponsored PMS studies are scientifically credible and truly undertaken to further the understanding of a product, they can enhance a company's reputation in a therapy area. Through meetings and dissemination, they provide an opportunity to further develop relationships that the sponsor company has with physicians. This is especially so in countries where regulations allow sales representatives to be the 'face' of a study, for example Germany. The results from the study can enhance a product's lifecycle in several ways, including providing 'new news' to disseminate at congresses and in peer reviewed journals, and potentially providing data to highlight points of parity and points

of differentiation versus alternative therapies. PMS studies also provide companies with an opportunity to gain additional information in terms of health outcomes and health economics.

CONCLUSION

Launching a drug on the market can potentially be considered an uncontrolled experiment on the general population, especially when it comes to better understanding the safety profile. PMS studies allow pharmaceutical companies (and others) to develop a more regulated and considered approach to gaining further important safety data in a broad population and can assist in identifying rare and potential adverse drug reactions. ♦

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