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Importance of Benefit Risk Assessment throughout the life cycle of a medicinal product

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Abstract

Pharmacovigilance (PV) is the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug related problem. Its aims are not only to enhance patient care and patient safety but also to support public health programmes by providing reliable, balanced information for the effective assessment of the benefit-risk profile of medicinal product. The safety profile of a drug is established by analysing individual cases and aggregate reports. The cumulative information, obtained from these reports, are used by the pharmacovigilance professionals in the detection of potential safety signals by monitoring evolving trends through various methods including qualitative and quantitative methods which includes statistical outputs. Identification of signals and risks is crucial for patient safety and involves ongoing monitoring of drugs to ensure they remain safe for use, especially since previously undetected adverse events can occur at any time. Proactive signal management and risk management throughout a medicinal products life cycle is the central element of the scientific assessment of a marketing authorisation application and regulatory agencies base their decisions for safer drugs to be retained and harmful drugs withdrawn by taking adequate measures.

INTRODUCTION

No effective medicine is without risk and the use of medicines has become more complex than ever before! While medicines bring significant benefits, there are also inherent risks to public health and patient safety mainly due to adverse reactions. Adverse drug reactions (ADRs) are an important public health issue because of high morbidity, mortality and cost that they generate [1]. Specifically, every medicine can have both wanted and unwanted effects which may occur in some or all patients. It is precisely for this reason that the benefits of medicinal product should always be weighed up against its risks and failing to manage the risks may lead to crisis situations with harmful consequences for patient safety and public health. Because of the strong impact in public health, regulatory authorities (RAs) worldwide have raised the bar and have implemented new pharmacovigilance legislation to protect public health by reducing the burden of ADRs through the detection of safety signals. Although, signal detection activities have mainly been performed based on spontaneous reporting databases, new pharmacovigilance legislation underlines the relevance of other sources of information e.g. scientific literature, epidemiology, large automated databases for the evaluation of the benefit–risk balance

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of medicinal product.

It is well known, that not all safety issues relating to a medicinal product are identified during clinical trials and very little is known about the safety profile before it comes on the market. Even though randomized controlled trials (RCTs) are the gold standard for assessing the efficacy of drugs and vaccines, it is not necessarily so for drug safety where narrow well defined patient inclusion criteria and inadequate power to detect either multiple or rare adverse events is a major limitation. Hence, at the time of approval of a medicinal product, knowledge of the full benefit-risk profile is incomplete thus making it more important to monitor the risks and benefits of medicinal products post-approval and throughout the product life cycle. Some risks become apparent only after approval of a medicinal product and vaccine, when it is used in millions of patients in the "real world" population. In real life, a medicinal product is used in larger numbers of patients, in different types of patients (e.g. elderly patients, children, patients with more severe or even milder disease, patients on other medications which could interact etc.) and for longer periods of time, which can change the risk profile of the product substantially.

Signal Management in Pharmacovigilance

One of the main objectives in pharmacovigilance is proactively identifying previously unknown adverse effects that may not have been identified in pre-marketing clinical trials. The mechanism through which this exercise of finding unknown and rare adverse events is done is through proactive signal management. The signal management process can be defined as "the set of activities performed to determine whether, based on an examination of individual case safety reports (ICSRs), aggregated data from active surveillance systems or studies, literature information or other data sources, there are new risks associated with an active substance or a medicinal product or whether known risks have changed" [2]. The signal management process include all steps from initial signal detection; through their validation and confirmation; analysis and prioritisation; and signal assessment to recommending action, as well as the tracking of the steps taken and of any recommendations made.

Signal detection methodologies in clinical trials and post-marketing

Multiple methods exist for signal detection activities but there is no gold standard. However, the signal detection methodology falls broadly under two components and groups namely post-marketing and clinical trial data:

i. Qualitative method: In this method, a case-by-case manual review of individual case reports or individual CIOMS forms is undertaken for a given period and a thorough analysis of the cases is done mainly by an assessor preferably a pharmacovigilance physician. No comparison is made with cumulative data in this method.

ii. Quantitative method: This method utilises statistical methods to identify drug-event pairs or frequent combinations of a drug and an event that occur with disproportionately high frequency in large spontaneous databases. Traditional quantitative methods used in spontaneous reports data have included reporting odds ratio (ROR), proportional reporting ratio (PRR) and Bayesian techniques which are used by several marketing authorisation holders (MAHs). With the development of several administrative health claims databases, additional methods such as sequence symmetry analysis (SSA) are also employed routinely to confirm and validated the signals. Hence, quantitative method utilises statistical outputs that helps in data mining and analysis of signals. Quantitative method is most useful on post-marketing data and for large, pivotal late stage trials or pooled studies.

Advanced Statistical Signal Detection Methods:

There are a few advanced statistical signal detection methods that are used for drugs in development and undergoing clinical trials. One of the statistical signal detection methods is the Bayesian Logistic Regression for investigating risk factor effects on occurrence of events/issues. In this method, identify events occurring with disproportionate frequency in subjects exposed to study drug. Events that are not 'expected' based on drug class, pre-clinical research, experience in earlier studies are investigated in detail as sufficient data is available through pooling. Another method that can be used is the Bayesian Issue Cluster Mining in which distance between each pair of issue is determined to find the shortest distance between each pair

i. Detecting Signals from Clinical Trial Data: In clinical trials, data standards make it possible to automate statistical outputs to systematically explore safety issues and generate hypotheses. To detect signals in clinical trials several techniques such as 2 x 2 table analyses or logistic regression after blind is broken is often used. However, this depends on effective visualizations to identify potential signals and outliers. Bayesian models can be helpful for multivariate estimation of possibly related adverse events (AEs). Also, searching for syndromes or clusters such as different AEs in the same patients associated with treatment and subgroup effects can be detected across the data through medically related adverse events.

ii. Detecting Signals in Blinded Data: One of the challenges in clinical trial data is detecting signals from blinded data. In order to detect signals from blinded data in clinical trials, aggregate blinded data to identify outliers and anomalies is conducted, where the same principles of aggregate visualization with drilldown to the case level is undertaken. It is also necessary to build surrogate comparator populations from appropriate past studies, so that size can be comparable and it is suggested that up to five times larger than the current study population should be used. It is therefore advisable to select data with similar treatment periods or comparable time windows exposure and subject exposure days rather than subject counts as denominator. Lastly, Bayesian shrinkage methods reduce imbalancing effect of outliers and this provides a more trusted signal. It is better to use statistical screening to generate hypotheses and use techniques such as logistic regression to adjust for age, gender, medical history and identify covariate effects.

Once a signal has been detected, the signal is then validated, analysed and prioritized. The validated signals are included in Risk management plans to optimize the benefit risk balance for a medicinal product

which are used for benefit risk assessments. Effective lifecycle safety management will require standard data, advanced tools and multiple sources of evidence. Once the risks are identified, the adverse drug reactions are then added to the Reference Safety Information documents e.g. Investigators Brochure (IB), Company Core Data Sheet (CCDS), Summary Product Characteristics (SmPC); US Prescribing Information (USPI) and others.

Risk Management Process: Risk management in simple terms is a proactive approach of assessing and minimising risks that are detected through signal management activities. Per EU definition risk management is "a set of pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to medicinal products, including the assessment of the effectiveness of those activities and interventions"[3].

Risk management process consists of identifying and characterizing the nature, frequency, and severity of the risks associated with the use of a medicinal product, throughout a product's lifecycle, from the early identification of a potential product, through the pre-marketing development process, and after approval during marketing. Pre-marketing risk assessment is the first step in this process, and it focuses on risk assessment prior to marketing mainly during clinical development in all phases of clinical trials. Regulatory authorities recommend that right from the start of development of a medicinal product; MAHs need to pay careful attention to the overall design of the safety evaluation. Potential issues that may be suspected because of pre-clinical toxicological data or because of effects of related drugs should be targeted for further and detailed evaluation. As it is impossible to predict every important risk, MAHs should refine and modify safety evaluations as more data is received throughout the phases of clinical development and classify the risks as: identified risk – adequate evidence of an association between the medicine and risk occurrence; potential risk – there is some basis for suspicion of an association between the medicinal product and the risk occurrence though it is not confirmed and lastly missing information – when there is insufficient or no data and additional data or evidence is needed to confirm the risk. This is essential in analysing and further understanding the actual risks of the medicinal product in detail. The strategy for risk management is thus based on the following and described below in Figure1:

Safety profiles: All risks (identified or potential) are compiled, along with a record of what is missing in terms of safety information.

Risk assessment or pharmacovigilance plan: This is the plan for further identifying, characterizing, and assessing risks. It contains both routine and additional pharmacovigilance activities.

Risk Management Plan (RMP): This is the plan for minimizing the risk; it is an integral part of the risk management plan as described in Figure 1 below. It contains both routine and additional risk minimization activities.

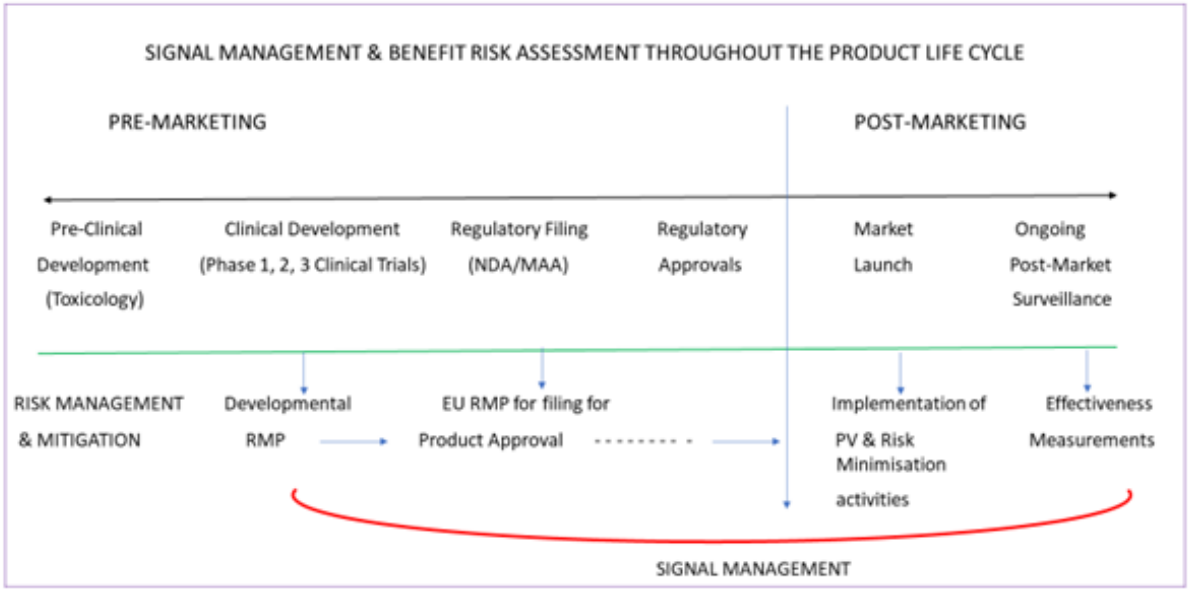
Challenges for the future

One of the main challenges of signal management in the context of benefit risk assessment is how to detect potential safety issues early during the clinical development phases and the analysis of the ever increasing quantity of the data effectively. The other challenge is how to get good quality and complete data from the individual case safety reports (ICSRs) for robust analysis and evaluate potential signals quickly and how best better methods in signal detection could be applied in emerging safety issues. This includes especially consistent and accurate MedDRA coding of event terms which is an important and key component of effective signal detection and benefit-risk assessment process.

CONCLUSION

Benefit Risk assessment is a complex activity within pharmacovigilance that includes all components of proactive Signal management and Risk

Figure1: Signal Management & Benefit Risk Assessment Throughout the Product Life Cycle



Management throughout a medicinal products life cycle and this is the central element of the scientific assessment of a marketing authorisation application. This increasingly complex activity within the clinical development process is necessary to enhance the benefit-risk balance of a medicinal product in real-life. Benefit risk assessment including signal management and risk management can be challenging and expensive, however, it is an important aspect on which regulators decide the marketing authorization application of a product. Signal detection is an ongoing dynamic process where no single method will meet all needs and all potential signals need to be systematically investigated appropriately and addressed. There is no gold standard method available for either signal management or benefit risk assessment; hence it is imperative to develop better multivariate methods of signal detection that can aid in effective benefit risk assessment. Lastly, it is advisable to include combination of both robust qualitative and quantitative methodologies to fully include all aspects of benefit-risk assessment throughout in the life cycle management of a medicinal product.

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