Methods

Pharmacovigilance Principles: *The Building Blocks of Benefit-Risk Assessments*

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ABSTRACT

A medicinal product must demonstrate a favorable benefit-risk balance to remain on the market. That the benefits of use outweigh the risks is established using analyses referred to as *benefit-risk assessments,* which are conducted on an ongoing basis throughout the lifecycle of a medicinal product. While fundamental to maintaining a product's marketing authorization, few regulatory guidance documents have been developed to provide information on the specific content and structure of a benefit-risk assessment. This paper aims to provide an overview of the key concepts in pharmacovigilance that contribute to the creation of a structured benefit-risk assessment, particularly through qualitative analysis.

KEYWORDS

Pharmacovigilance; Benefit-risk assessments; Drug safety profile

WHY PHARMACOVIGILANCE IS NEEDED

What makes a drug safe to use? How do we know that it is safe to use? When are the potential side effects worth the risk? These questions drive the practice of pharmacovigilance, the art and science of drug safety monitoring performed throughout the lifecycle of a medicinal product. From the time a drug is first developed in a laboratory, its safety is documented, studied, and weighted against its relative benefits.

In an ideal world, all drugs would be safe and effective, easy to use, and have no side effects. In reality, however, all medications have at least the potential to cause some side effects. Pharmacovigilance's ultimate goal is to ensure that the only drugs available for use provide more benefits than risks. This is achieved by continuously assessing and reassessing the evidence for drug safety relative to drug efficacy.

Pharmacovigilance is defined by the World Health Organization (WHO) as "the science and activities relating to the detection, assessment, understanding, and prevention of adverse effects or any other drug-related problem. (1) In its modern form, pharmacovigilance was developed largely as a response to what is often referred to as "the thalidomide tragedy" that unfolded in the late 1950s and early 1960s.Thought be safe and effective means of curbing morning sickness, thalidomide was prescribed to pregnant women across 46 countries over several years. By 1961, doctors in Australia and Germany simultaneously and independently recognized a significantly increased number of children born with a spectrum of limb deformities known as phocomelia. (2) They recognized that the increasing trend toward the use of thalidomide was correlated with (i.e., happening at the same time) and appeared to be *causally* associated with the significant increase in cases of what is usually a rare malformation. Health authorities worldwide quickly withdrew the drug, but much damage had already been done: more than 10,000 children had

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been born with thalidomide-associated limb defects. (2) The thalidomide tragedy remains a constant and sobering reminder of the importance of robust pharmacovigilance practices.

BUILDING BLOCKS OF PHARMACOVIGILANCE

Let us start with a few terms frequently used in pharmacovigilance. The terms "drug," "medicinal product," "drug substance," "compound," and "active moiety" are often used throughout pharmacovigilance science and activities. While they appear to be used interchangeably, some subtle but important distinctions between these terms should be noted. The "compound," "drug substance," or "active moiety" (a.k.a. "active ingredient") is the chemical constituent of a drug that is intended to provide its medicinal effect. (3) The terms "(drug) product" and "medicinal product" refer to all parts of a given delivery system for the active moiety. (4) For example, paracetamol is the active moiety that can be found in drug products, including tablets, syrups, and others, both by prescription and over-the-counter.

Once the evidence for product safety has been established *in vitro* and in non-human models of study, formal clinical trials and spontaneous reporting systems allow for the collection of safety data in humans. Whether referred to as patients, subjects, or "cases," most safety data used in pharmacovigilance arise from using medicinal products in humans. This data includes any unwanted effects (a.k.a. "side effects,") which are called either "adverse drug reactions (ADRs)" or "adverse effects (AEs)." While seemingly similar, a significant difference exists between AEs and ADRs; an ADR requires that there exists at least a reasonable possibility of a causal association between the drug and the reaction.

During drug development and clinical trials, "all noxious and unintended responses to a medicinal product related to any dose" should be considered ADRs. (5) Once the product has an approved dose and indication for use, an ADR should be defined as "a response to a drug which is noxious and unintended and which occurs at doses normally used in [humans] for prophylaxis, diagnosis, or therapy of disease or modification of physiological function." (6) Conversely, an AE is "any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment." (5) Whether a potential causal association has been established (i.e., ADR) or not (i.e., AE), both ADRs and AEs provide important information helping to establish the recognized safety profile of a drug. While the difference between AEs and ADRs has been clearly established, the significance of each type of event has been interpreted differently in small but important ways by various regulatory bodies. For example, spontaneous reports for marketed products must be reported to the EMA only if they contain ADRs. In contrast, the United States (US) requires reporting all AEs in such cases.

Any unwanted effects (i.e., AEs, ADRs) occurring in humans can be referred to as a "case" of the given event of interest. "Subjects" are those healthy volunteers who participate in the earliest phases of clinical trials that focus only on the drug's ability to be safely administered to humans. In subsequent phases, where safety and efficacy are assessed, the drug under study is provided to patients with a particular health condition the drug is designed to treat. While clinical trials provide close monitoring of patients using the drugs under ideal conditions, spontaneous reports occur 'in the wild,' (i.e., under real-world conditions of use) after a drug has been approved for use (i.e., "post-marketing").

The overall level of patient exposure is also important to understanding a drug's safety profile. Although clinical trials involve hundreds and sometimes thousands of patients, some rarer side effects do not become apparent until a drug has been used in tens- or hundreds of thousands of patients. This makes a "post-marketing" safety review essential to elucidate a drug's complete safety profile.

PHARMACOVIGILANCE PRINCIPLE AND BENEFIT-RISK ASSESSMENT

Benefit-Risk Assessments (BRAs) are fundamental to pharmacovigilance. A BRA is any analysis of the utility of a medicinal product for a given indication taking into account the potential drawbacks. (7) They help contextualize the risks associated with a medicinal product, identified via product safety assessments. It can be helpful to visualize BRAs as the result of piling a scale with all the evidence supporting product efficacy (benefits) opposite from the evidence for product safety (risks), as demonstrated in Figure 1. As per internationally accepted guidelines, only products demonstrating a favorable benefit-risk balance (BRB), a tipping of the scales toward the benefits of the drug, are allowed to remain on the market. (8)

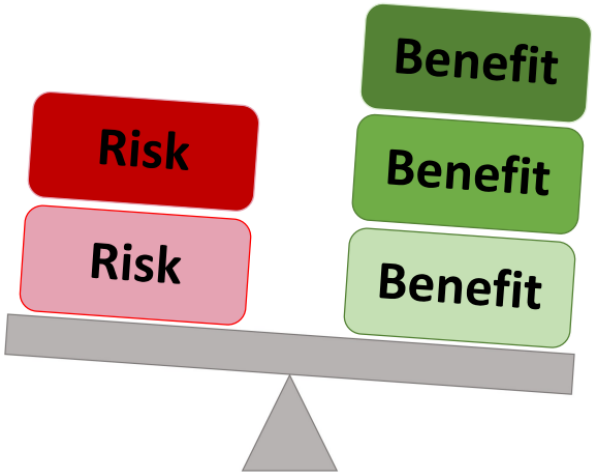

Figure 1. Benefit-risk assessments weigh a product's risks against its benefits.

Pharmacovigilance is a relatively new discipline in the pharmaceutical industry. While its research and develop-

ment may involve other disciplines, a product's pharmacovigilance activity may require inputs from multiple stakeholders in social, biomedical, and scientific communities. Product marketing authorization holders (e.g., the pharmaceutical company responsible for the manufacture and distribution of the drug) are the parties primarily responsible for conducting pharmacovigilance research and development activities. Local and regional health or Regulatory Agencies (RA) oversee these activities. The guidelines for pharmacovigilance activities to which Health Authorities (HA) adhere in many countries are those outlined by the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH). (9) The examples provided by regions with robust pharmacovigilance systems, such as those found in the European Union (EU) and the US, provide significant additional information on the application of ICH guidelines. (10) As the analysis and dissemination of data collected by HAs may take time, the information on product safety available directly from Marketing Authorization Holders plays a crucial role in ensuring product safety.

Every aspect of a drug's safety profile contributes to the balance of benefits and risks ascertained for that drug on an ongoing basis. Periodic BRAs can be developed as standalone documents that formalize and clarify the weight of the evidence supporting a product's stated BRB. These are often available as BRAs included in important regulatory documentation and communications. In 1998, the Council for International Organization of Medical Sciences (CIOMS) IV working group developed a landmark guidance document assessing safety signals in evaluating the BRB for marketed drugs. (11) While this and other guidelines provided by HAs and RAs provide necessary information relevant to BRAs, the specific steps involved in creating a BRA may not always be readily apparent.

This paper aims to provide an overview of the key concepts in pharmacovigilance that contribute to the creation of a structured BRA (sBRA). In a separate publication, we also provide an illustrative example of the fundamental role an sBRA plays in clarifying the benefits and risks for even well-established products.

BENEFITS MUST OUTWEIGH RISKS

Evidence of efficacy

In every BRA, the weight of the evidence for beneficial effects relative to the uncertainties regarding efficacy and safety must be clearly established. Evidence about efficacy is generally obtained during clinical development and the clinical trial phases I-III of the drug approval process (Figure 2). Nevertheless, data obtained during post-marketing use, either through phase IV clinical studies or through other data collection methods such as product registries, meta-analyses, published case reports, ongoing non-clinical studies, and spontaneous reporting systems, can also provide insights as to product efficacy for specified indications. The levels of evidence available from these various sources must be considered concerning claims of product efficacy.

Also important in determining the weight of evidence in favor of a product's benefits is the availability of alternative therapies. Even if other drugs on the market are approved for the treatment of the same indication, these may not be available in all countries or may not have been proven sufficiently safe in specific populations (e.g., children, patients with hepatic impairment, etc.). There may also be data to support the superior efficacy of one treatment over the others, often indicated as "first-line treatment" for the given indication. Therefore, the absolute and relative availability of alternative therapies can be a significant, if evolving, factor determining the benefits of a given drug.

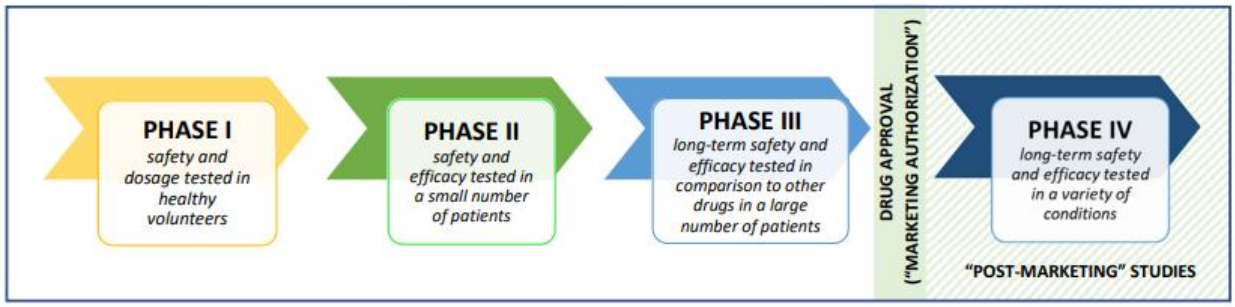

Figure 2. Overview of the drug approval process

Identification of safety concerns

Possible risks can be identified through "signal evaluation," a significant pharmacovigilance activity. A pharmacovigilance "signal" has been formally defined as "information that arises from one or multiple sources (including observations and experiments), which suggests a new potentially causal association, or a new aspect of a known association, between an intervention and an event or set of

related events, either adverse or beneficial, that is judged to be of sufficient likelihood to justify verificatory action." (12) While a signal may arise from any number of sources, including observations during clinical experience or findings from non-clinical laboratory data, they all pertain to evaluating the nature and significance of AEs and ADRs occurring after the use of a product, in consideration of what may be expected based on existing knowledge about that product. (13)

A signal may also be a concern by a drug safety professional about a possible causal link between a drug and an event. Any potential signal topic must undergo validation and confirmation before a formal evaluation. This includes considering factors such as the magnitude and clinical significance of the event and the patient factors involved. Potential alternative explanations for the event as suggested by the context (e.g., patient demographics, a disease being treated, etc.) should also be considered in an attempt to "strengthen" the signal and justify (or not) further verificatory action. For example, atrial fibrillation (AF) is a heart condition that becomes more common with age and can occur with other cardiac conditions. Therefore, an event of AF occurring in an elderly patient may be less likely to suggest a causal association to a given medicinal product than if the same event occurred in a child. Suppose the drug is indicated for use only in patients with a cardiac pacemaker. In that case, the patient's underlying medical condition may account for the events of AF, irrespective of age, preventing the need for signal assessment. Alternatively, the use of the drug exclusively in young patients without prior cardiac conditions may 'lower the threshold' to triggering a signal after observing events of AF. A signal may be raised by the occurrence of a new event or a change in frequency, nature, or severity of a previously observed AE or risk. Signals may pertain to a single product or several products, such as those in the same drug class or with the same mechanism of action.

Signals undergo an evaluation to determine the level of evidence indicating a causal association to the product. The outcome of a signal evaluation is either refutation of the signal or adjudication as a risk. Risks are then characterized as either potential or identified, and some may be classified as "Important" (See Box 1). Risks classified as important are those which may alter the benefit-risk balance unless sufficient countermeasures are adopted. Specifically, "Important Identified Risks" may impact the benefit-risk balance, whereas "Important Potential Risks" could alter the benefit-risk balance if they became identified risks. (14)

Box 1 Concepts relevant to a product's safety concerns

Identified risk	"An untoward occurrence for which there is adequate evidence of an association with the medicinal product of interest." In other words, identified risks are those unintended effects known to be caused by a drug. They are often referred to as *adverse drug reactions* or, more colloquially, *side effects*.
Potential risk	"An untoward occurrence for which there is some basis for suspicion of an association with the medicinal product of interest but where this association has not been confirmed." In other words, potential risks are those unintended effects seen, for example, with other drugs in the class or animal models but which have not yet been observed in humans with sufficient evidence to suggest a causal association.
Important risk	Both identified risks and potential risks may be further characterized as important. Important risks are those that can have an impact on the BRB of a product or have implications for public health. An important potential risk would impact the BRB if the risk were to become identified.

Establishing and characterizing a drug safety profile

A product's safety profile comprises all known and suspected risks associated with a drug or product exposure. The safety profile pertains to the use of a drug in both the "target population" (i.e., the approved indication for use) and in "special populations" (e.g., the elderly, patients with renal impairment, etc.). It should specify differences between the types, nature, frequency, or severity of AEs experienced by patients in special populations compared to patients in general.

While a drug's safety profile encompasses all of its established safety information, a drug's list of "safety concerns" indicates those risks which have the most significant known or potential impact on the BRB of the drug. The safety concerns include the important identified risks, important potential risks, and missing information, which are described in Box 1. All safety concerns should be well-characterized, including information on the frequency of the event, the seriousness, the severity and nature of the risk, the background incidence/prevalence in the general population, risk groups/factors, potential mechanisms, preventability, impact on the individual patient/public health and risk minimization measures. The safety concerns included in a product's risk management plan (RMP) are addressed prospectively with risk mitigation activities or ongoing studies, all of which comprise the "safety specification." Of note, identified and potential risks

that have not been characterized as “important” are outside the scope of the list of safety concerns and specifications.

ONGOING BRA vs. STRUCTURED BRA

Throughout a product’s lifecycle, continuous monitoring of AEs and efficacy contributes to the ongoing development of the drug's safety profile. With new information available regarding a drug's safety or efficacy, the Marketing Authorization Holder has an ethical and legal obligation to determine if the drug’s BRB remains positive. RAs and HAs in the countries where there are marketing authorizations for the drug are charged with confirming a consensus on a favorable product. This consensus is regularly revisited based on data that the Marketing Authorization Holders provide and data obtained independently. Data supporting such consensus may be derived from numerous sources, including HAs in other countries or regions. The US FDA and European Medicine Agency (EMA) are two important sources of such information.

While a summary BRA for a product is regularly included in the routine and *ad-hoc* pharmacovigilance documenttation, a stand-alone sBRA provides a detailed analysis that supports and clarifies assertions of a positive BRB. Updated sBRA are typically developed at the time of marketing authorization approval or renewal. It is also advisable that an sBRA be performed upon marketing authorization transfer and when new important risks are identified.

The challenge for Marketing Authorization Holders conducting sBRAs is that there is no single standard methodology for BRAs defined by the regulatory agencies. The format used and recommended by the authors for sBRAs is described below.

STRUCTURED BRA FORMAT: QUALITATIVE AND QUANTITATIVE TOOLS

The sBRA is a systematic presentation of the weighted evidence for a product's available benefits, risks, and uncertainties considering the therapeutic and regulatory context. Overall, an sBRA is a descriptive tool; however, quantitative methods complement the development of the sBRA. Although the data contained within should be objective, the overall conclusion of an sBRA may include independent (subjective) judgment by relevant professionals. (15)

Since the 1980s, there has been a growing effort to develop more robust quantitative tools to complement the descryptive sBRA. While no single method or format is common today, many tools and techniques have been developed to standardize BRAs. This includes the qualitative approaches of “PrOACT-URL (Problem, Objectives, Alternatives, Consequences, Trade-Offs, Uncertainties, Risk, Linked decisions) and the BRAT (Benefit Risk Action Team) method. Some quantitative methods include the "Multi-Criteria Decision Analysis" and "Stochastic Multicriteria Acceptability Analysis." (7) While these or other tools with the ability to ‘rate’ or ‘score’ the benefits and risks of a product may seem appealing, the scoring systems used can only be considered internally relevant and have no ready equivalent allowing purely numerical comparison across drug products. This is one of the reasons why qualitative and quantitative assessments are complimentary, not mutually exclusive.

The recently released draft guidance on BRA from the US FDA only references quantitative methodologies regarding patient experience data. In alignment with the US FDA programs on patient-focused drug development, this new ‘guidance for industry’ document emphasizes the inclusion of quantitative patient experience data as integral to developing a primarily qualitative BRA (15). The specific contents and structure of an sBRA recommended by the authors will be described separately.

FURTHER CONSIDERATIONS: A GLOBAL PERSPECTIVE OF PHARMACOVIGILANCE

sBRAs contribute to pharmacovigilance practices across the lifecycle of a product. Even for well-established products, the BRB can shift over time as new data emerge from greater patient exposure, off-label use, specific age groups, expanded indications, regional clinical practices, new formulations, and new registries even for well-established products. Concurrent updates should support enhanced clarity and dissemination of clinical knowledge. In pharmacovigilance, the Medical Dictionary for Regulatory Activities (MedDRA), updated twice yearly, is a lexicon that provides a common language for health conditions and AEs. (16) Properly using this standardized terminology across pharmacovigilance activities helps ensure appropriate comparison and compilation of data from diverse sources even as the understanding and practice of medicine continue to evolve and expand.

The evolution of clinical medicine can impact the BRB as new clinical entities are recognized. For example, definitions of what constitutes "allergies” versus “hypersensitivities” have evolved as understanding the mechanisms of immunogenicity evolved. Additionally, awareness of other recently identified clinical conditions, such as severe cutaneous adverse reactions (SCARs), have been increasingly recognized as AEs potentially impacting the BRB of medicinal products. Over time, expectations from medicinal products can also evolve. This can arise due to scientific advances and increased regulatory expectations. Public expectations can also change due to increased awareness of and access to scientific and medical information. Physicians may even find it challenging to remain the clear source of expert advice when patients have access to much medical information. For example, the deluge of data available to the global public on Covid-19 prevention and treatment likely has increased the awareness of and need for ongoing assessments of existing medicinal products. Evaluations such as those conducted on existing drugs for the treatment of Covid-19 (as well as for the

newly-developed Covid-19 vaccines) have publicly illustrated how qualitative and quantitative data contribute in a complementary manner to potentially previously unrecognized benefits and risks of even well-established medicinal products. (17,18)

The BRA is also influenced by external factors driving local standards in clinical care, which can vary in small yet important ways. For example, a drug that may be considered the 3rd line treatment in one country may be used as 1st line treatment in another due to factors such as a lack of access to safer or more effective drugs. Such situations can occur due to local marketing authorization status, price, geosocial, or other non-medical limitations (e.g., lack of sufficient refrigeration in hot climates). The withdrawal of thalidomide from the global market occurred at varying stages due to differing rates of dissemination of medical information across the 46 countries affected. Pharmacovigilance professionals must take into consideration that such changes in external influences on clinical practice may also alter the BRA.

The total level of patient exposure incurred from relatively extensive or long-term use is another important factor for fully elucidating the safety profile of medicinal products. Higher exposure rates provide larger data sets for analysis, increasing confidence in the significance of the observed trends. It can even allow very rare events (e.g., occurring in <1 per 100,000 patients) to become observable. Significant patient exposure can occur after a drug has been on the market for a significant time or can occur rapidly due to popularity or use for a common condition. For example, high exposure rates (and a robust pharmacovigilance system) recently contributed to the impurities in the excipients of the relatively new but popular antacid, ranitidine. (19) Rapid recognition of and response to such events can help to enhance public awareness of and confidence in the drug safety surveillance systems at work in their communities.

Even if the utility of sBRAs enter public awareness, exemplar documents remain challenging to be identified; the detailed sBRA prepared by Marketing Authorization Holders and HA during safety evaluations are often not publicly available. Instead, key points may be summarized in public assessment reports, including elements of a full sBRA. (20–24) High exposure rates with decades of use across commonly-occurring indications has contributed to surprising new information regarding the safety profile of one of the world's most popular drugs: acetaminophen. These important new findings will be discussed separately, which perfectly illustrate the importance of robust pharmacovigilance systems and ongoing sBRAs.

CONCLUDING THOUGHTS AND NEXT-STEPS

Pharmacovigilance practices have brought immeasurable benefits to human health and society. The tools to perform routine pharmacovigilance activities are well-established and subject to the evolutionary processes inherent in scientific practices. As one of the tools essential to pharmacovigilance, benefit-risk assessments can become even more fruitful and robust when following a formally structured format. It helps to assure that all factors contributing to the overall BRA are included and considered. HAs and Marketing Authorization Holders may further consider the collaborative development of clear and robust sBRA templates and guidelines to enhance the capabilities of robust pharmacovigilance systems.

ABBREVIATIONS

ADR	Adverse Drug Reaction
AE	Adverse Event
AF	Atrial Fibrillation
BRA	Benefit-Risk Assessment
BRB	Benefit-Risk Balance
CIOMS	Council for International Organization of Medical Sciences
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration
HA	Health Authority
ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
MedDRA	Medical Dictionary for Regulatory Activities
RA	Regulatory Agency
RMP	Risk Management Plan
SCAR	Severe cutaneous adverse reactions
US	United States (of America)
WHO	World Health Organization

CONFLICT OF INTERESTS

The authors declare no conflict of interest regarding the publication of this paper.

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