Chapter 5
Safety Signal Detection in the Drug Development Process

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ABSTRACT

Drug development is a complex set of inter-linked processes in which the cumulative understanding of a drug's safety and efficacy profile is shaped during different learning phases. Often, drugs are approved based on limited safety information, for example in highly at risk or rare disease populations. Therefore, post approval, regulatory organizations have mandated proactive surveillance strategies that include the collection of reported adverse events experienced by exposed populations, some of whom may have been on treatment for extended periods of time. Analyzing these accumulating adverse event reports to understand their clinical significance, given the limitations imposed by the methods of data collection, is a complicated task. The aim of this chapter is to provide the readers with a general understanding of safety signal detection and assessment, followed by a description of statistical methods (both classical and Bayesian) typically utilized for quantifying the strength of association between a drug and an adverse event.

INTRODUCTION

The successful development, registration and marketed use of a new pharmaceutical entity require regular reappraisal of its risk-benefit profile, throughout its life-cycle. An intimate understanding of the real or potential risks to patients of taking a pharmaceutical intervention will inform how it is formulated, packaged, labeled, prescribed and taken by patients, including how known risks are managed or avoided. A key component of a marketing authorization is the agreed strategy for identifying new risks and how emergent risks will be characterized and managed once the pharmaceutical product is launched; in the context of risk management, what remains *unknown* about the product becomes as important as that

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which is known. Indeed, a failure to present an adequate strategy to deal with uncertainty in relation to risk is likely to result in the rejection of an application to market a product.

The safety profile of a new pharmaceutical entity evolves over the drug development process and new risks continue to be identified once it is launched onto the market. The information upon which decisions related to safety are made may vary considerably, depending on the life-cycle stage of the product and the methods of detecting and evaluating new risks will differ based on the type, quantity and quality of the available data. In the early stages of drug development, the number of exposed subjects will be small, although the quantity of information on each may be plentiful and the quality high in terms of how the data are collected and recorded. In the latter stages of drug development, the number of exposed patients will generally be much higher although the amount of information collected on each patient may be less. Even in the largest phase 3 trials, the quality of the data is still subject to appraisal and control and it is usually possible to obtain further information to help characterise any emerging safety concerns. Once on the market, patient exposure to a product is likely to grow massively in comparison with that seen in development; even if the quantity of data from these patients is growing exponentially, there will only limited ability to directly influence the quality of the information coming from marketed use and in most cases, the information content itself may be sparse. In this chapter we will explore how a range of more or less innovative and established statistical methods can be employed to enhance risk identification over the life-cycle of product with a particular focus on those that are amenable to automation and computer-aided screening of large datasets as encountered in the post-marketing setting.

BACKGROUND

For the sake of clarity the following definitions are assumed throughout this chapter:

An *adverse drug reaction* (ADR) is `a noxious and unintended response to a medicinal product for which there is a reasonable possibility that the product caused the response.' (International Conference on Harmonisation, 1994)

An *adverse event* (AE) is defined as `any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product which does not necessarily have a causative relationship with this treatment.'(International Conference on Harmonisation, 1996)

Disproportionality analysis (DPA) is `the application of computer assisted computational and statistical methods to large safety databases for the purpose of systematically identifying drug-event pairs reported at disproportionately higher frequencies relative to what a statistical independence model would predict.'(J. Almenoff et al., 2005)

A *drug-event pair* is the combination of a medicinal product and an adverse event which has appeared in at least one case report entered into a spontaneous report [safety] database.(CIOMS Working Group VIII, 2010)

The *safety profile* of a drug or other therapeutic intervention can defined as the aggregate knowledge of the severity and frequency of adverse drug reactions and other risks related to the use of the intervention.

A *safety signal* is defined as `information that arises from one or multiple sources (including observations and experiments), which suggest 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.'(CIOMS Working Group VIII, 2010)