Monitoring product safety in the postmarketing environment

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Abstract: The safety profile of a medicinal product may change in the postmarketing environment. Safety issues not identified in clinical development may be seen and need to be evaluated. Methods of evaluating spontaneous adverse experience reports and identifying new safety risks include a review of individual reports, a review of a frequency distribution of a list of the adverse experiences, the development and analysis of a case series, and various ways of examining the database for signals of disproportionality, which may suggest a possible association. Regulatory agencies monitor product safety through a variety of mechanisms including signal detection of the adverse experience safety reports in databases and by requiring and monitoring risk management plans, periodic safety update reports and postauthorization safety studies. The United States Food and Drug Administration is working with public, academic and private entities to develop methods for using large electronic databases to actively monitor product safety. Important identified risks will have to be evaluated through observational studies and registries.

Keywords: pharmacovigilance, product safety, signal detection

Introduction

Developing pharmaceutical products is costly in both time and resources. It has been estimated that a pharmaceutical company spends approximately one billion dollars on developing a product and it can take many years to take a compound from discovery to regulatory approval and launch. Although a great deal of information on the product’s safety and efficacy is gathered during clinical development, it is not possible to describe fully the safety profile of the product in premarketing clinical trials. A number of drugs such as Bextra® (valdecoxib for Stevens–Johnson syndrome), Rezulin® (troglitazone for hepatotoxicity) and Vioxx® (rofecoxib for myocardial infarctions) have been withdrawn from the market because of adverse reactions that were unknown or not fully characterized when the drug was approved. It is important for patients and pharmaceutical companies alike to properly monitor product safety in the postmarketing environment, so that physicians know what the risks of the product are and how to prescribe the product appropriately and patients know how to take the product safely.

Monitoring product safety has been traditionally done by passive surveillance (voluntary reports) or the collection of spontaneously reported adverse events from healthcare providers and consumers following the administration of a medicinal product. With the development of computers and electronic medical records, it is now possible to conduct active surveillance (a proactive search) of adverse events whereby biopharmaceutical companies and regulatory agencies can search large databases of healthcare records to determine adverse events associated with the use of a medicinal product. Both systems have advantages and disadvantages, but together they provide a relatively effective way of monitoring product safety. Table 1 describes the data sources and activities that are used to monitor product safety in the postmarketing environment. Individual case safety reports can be reviewed individually, in an aggregate fashion, or in a case series to determine potential safety signals that need to be evaluated in formal epidemiological studies. Large databases can be used to look for statistical signals of disproportionality and to conduct observational studies to further identify and
characterize safety signals. This paper discusses the various activities conducted by biopharmaceutical companies and regulatory agencies to monitor product safety.

**Postmarketing reporting of adverse experiences**

The main source of safety information for newly approved drugs is the routine postmarketing surveillance of adverse experiences. Four major databases are used. The World Health Organization for International Drug Monitoring (Uppsala Monitoring Centre) has VigiBase™, which was started in 1968 and contains over 7 million individual case safety reports from 144 member countries [WHO 2012]. The United States Food and Drug Administration (FDA) has the Adverse Event Reporting System (AERS), which was started in 1969 and contains over 4 million reports [FDA 2011a], and the Vaccine Adverse Event Reporting System (VAERS) [VAERS 2013], which was started in 1990 and contains over 400,000 reports. The European Medicines Agency (EMA) has EudraVigilance, which was started in 2001.

All four are computerized information databases designed to monitor the safety profile of products in the postmarketing environment. They are passive, voluntary reporting systems that collect data from manufacturers, healthcare providers, consumers and the medical literature about adverse experiences that may be associated with the use of a medicinal product. These systems include serious, unexpected and related adverse experience reports from clinical trials, as well as spontaneous reports from healthcare professionals, consumers, lawyers, and others. It is important to emphasize that the reported adverse experience is temporally associated with the use of a product and may not necessarily be causally associated with the use of the product. Furthermore, since there are no standard medical definitions for adverse event terms used for collecting reports, and since the adverse event is coded using the terminology of the reporter, the event may not be accurately reported, particularly when it is reported by someone who is not a healthcare professional.

There are limitations and strengths to these reporting systems. They cannot be used to determine incidence rates of adverse experiences because of under-reporting of adverse events (lack of a good numerator) and because of an unknown number of patients taking the drug (lack of a denominator or population at risk of experiencing the adverse event). Furthermore, there are no data on comparable populations of individuals with the same underlying condition and who are not being treated by the medicinal product under surveillance. Given the inability to compute an incidence rate, pharmacovigilance specialists create reporting rates, defined as the number of reported adverse events divided by the amount of drug distributed. Although these reporting rates would be an underestimate of the true rate, they can be compared with known published rates in the general population. In addition, these passive reporting systems are not good at detecting events that may have a long latency period because prescribers and patients may not associate the events with an exposure years before. Similarly, events that are commonly occurring in the general population, such as myocardial infarction, may not be associated with a drug exposure.

One strength of these adverse event reporting systems is that they collect data on patients who

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would not normally be included in clinical trials. Traditionally, eligibility criteria for premarketing clinical trials exclude individuals with concurrent illnesses treated with concomitant medications or high risk individuals who should not receive the medicinal product, such as pregnant women or individuals with compromised immune systems. Another strength of postmarketing safety surveillance is that these systems collect data about rare events that may be associated with the use of the product. If similar individual rare adverse events are reported from throughout the world, these events would then become a cluster of events which could then be evaluated from an epidemiological perspective. Identifying groups of rare events also gives biopharmaceutical companies the opportunity to investigate these events in more detail by collecting additional information on individual cases that may be informative as to why certain individuals experienced the rare event. Another important advantage of these systems is that they identify issues of concern to the healthcare provider using the product. They serve as the voice of the prescriber and identify the issues that need to be evaluated in more formal epidemiological studies. If a biopharmaceutical company expects a healthcare practitioner to continue using its product, it needs to address these issues of concern.

**Interpretation of postmarketing adverse experience reports**

Not all spontaneous adverse events in the postmarketing environment are associated with the medicinal product being reported. A spontaneous report may be caused by the drug in question, by the underlying disease process being treated, by a concurrent illness or concurrent medications, or it could just be a random event that would occur in any population under observation. There are very few laboratory tests that one can use to determine if an adverse experience is associated with the use of a medicinal product. However, there are some situations where one can surmise with relative certainty that an event is associated with a drug, such as with anaphylactic shock or anaphylactoid reactions. It is also possible to show an association between certain adverse events and the administration of vaccines. For example, paralytic polio is associated with the administration of oral live attenuated polio vaccine [CDC, 2012]. This has been demonstrated when a recipient of the vaccine or a close associate of the recipient has contracted clinical paralytic polio and an isolate from the cerebrospinal fluid has been shown to be the same as the vaccine strain. Similar demonstrations for other adverse experiences have been shown with the live attenuated measles and varicella vaccines [Sharrar et al. 2001].

If there are no laboratory tests to determine whether an event is associated with the use of the medicinal product, then one has to use general epidemiological principles to determine if there is a possible association. It has to be demonstrated that the adverse experience of concern is more common in a group of individuals taking the drug compared with a group of comparable individuals not taking the drug. This entails collecting information from both individuals taking the medicinal product and from individuals not taking the product. The resulting analysis shows that, at a population level, an exposed group of individuals has a higher risk of the adverse event than the unexposed group; however, risk at the individual level cannot be determined. The inability to identify individual risk is especially difficult for adverse events that have a multifactorial etiology such as myocardial infarctions.

Although many adverse drug reactions are not reported by healthcare providers, serious adverse reactions are believed to be more likely to get reported. If a healthcare provider detects a serious adverse experience in a patient which cannot be explained, and if this adverse event occurred after the administration of a new drug or vaccine, they may report it to the pharmaceutical company to learn if other patients have had a similar reaction. Since many of the drugs withdrawn from the market or restricted in use are because of some degree of evidence from spontaneous adverse experiences reported in the postmarketing period, and since these reports are an important source of new information, it is important to collect complete and accurate data on every serious reported event. In order to properly interpret spontaneously reported adverse events, one has to have a good understanding of the pharmacological properties of the drug, an understanding of the natural history of the disease process being treated, and an understanding of random events that occur in any population under observation.

An initial step in evaluating groups of spontaneous reports is to tabulate a frequency distribution of all reported adverse events for that particular medicinal product generated either from a large external database or from the manufacturer’s own adverse event monitoring system. A review of this
list will identify serious adverse experiences and their frequency of being reported, and is used to identify adverse experience reports that need to be evaluated in more detail. In order to interpret these serious reports, it is frequently necessary to collect additional follow-up data on important variables related to risk using a focused data collection tool such as a questionnaire or a structured data collection script.

Some factors to consider in evaluating individual reports include the frequency of reports, the temporal association of the event with drug administration (the event occurs after the drug has been taken), the timing of the adverse event (an anaphylactic reaction should occur relatively quickly while the development of a cancer would require a longer latency period), a positive re-challenge event, consistency of the event with pharmacological properties of the drug or with other drugs in the same class, and consistency with other data collected during drug development. The evaluation of spontaneous reports should consider rare adverse events that are typically associated with drug use such as Stevens–Johnson syndrome, toxic epidermal necrolysis, or hypersensitivity reactions. These adverse events could alter the benefit–risk profile of the drug.

For those adverse events that need to be evaluated further, a case series can be developed and analyzed to determine the clinical spectrum of the adverse event and its outcome as well as its pattern of occurrence. Since the report is coded using the terminology of the reporter, the report may not be what it says it is. Therefore, a case definition should be created to make certain that the reported cases included in the case series analysis are the same disease condition. The individual reports that comprise the case series should be carefully reviewed and analyzed by examining the distribution of reports, using the epidemiological variables of person, place and time. The clinical characteristics of the cases need to be determined as well as the outcome of the event. Determining the characteristics of the individuals who developed the event, such as age, gender, medical history and concomitant medications, is important as is determining other potential risk factors. Since a case series has no control group, the analysis has to compare the distribution of cases with that observed in the general population. Are the cases occurring in the same age and sex distribution that one would expect or are the reports occurring in a different segment of the population? For example, the reported cases of multiple sclerosis in Merck’s postmarketing database that were reported following the distribution of hepatitis B vaccine have the same age and sex distribution as the cases of multiple sclerosis that occur in the general population, suggesting that these individuals may have gone on to develop multiple sclerosis even if they had not received the vaccine. Subsequent epidemiological studies have shown no association between hepatitis B vaccine and the onset or exacerbation of multiple sclerosis [DeStefano et al. 2002].

Disproportionality analysis

Spontaneous adverse experience reports in a large database can also be used to carry out a disproportionality analysis (or data mining or signal detection), which uses statistical or mathematical tools to identify potential safety signals [Bate et al. 1998; DuMouchel, 1999; EMEA, 2008; Evans et al. 2001; Faich and Morris, 2012; HMA and EMEA, 2012e]. Although there are different methodologies for disproportionality analyses, the methods are similar in that they all calculate an expected number of events that would occur based on the proportionate reporting ratio for all the other drugs in the database. This expected number is compared with the actual number of reports observed. A score generated by data mining quantifies the disproportionality between the expected and the observed product–event combination. The analysis can be refined by adjusting for age, year of reporting and indication. A product–event combination becomes a statistical signal when the disproportionality exceeds a predefined threshold.

A statistical signal just means that the observed number of reports is higher than expected for a particular drug–event combination. Statistical signals are frequently found because of the large number of comparisons made. A statistical signal of disproportionate reporting does not necessarily indicate that there is a signal to be further investigated or that a causal association is present. The statistical signal must be assessed to examine the evidence for a causal association between an adverse event and a medicinal product. A safety signal, from a pharmacovigilance prospective, is defined as information arising from one or more 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 verifactory action [HMA and EMEA, 2012a] This requires an evaluation of a statistical association from a clinical and public health perspective.

The strength of these types of analyses is that it is a systematic way for sponsors and regulatory agencies to identify potential risks of a drug from a large database involving a large number of adverse experiences and many hundreds of drugs. A major limitation of disproportionality analysis is that it creates a large number of statistical signals that then need to be evaluated from a medical perspective. Some of these potential safety signals could require considerable resources to evaluate and, therefore, criteria should be established to determine which signals need further evaluation. Safety signals that need to be further evaluated include serious adverse events, drug interaction signals, and adverse events that are biologically plausible or consistent with the drug’s mechanism of action. The evaluation should include a comparison with data collected in preclinical animal toxicology studies, with clinical trial data, and with data on other drugs in the same class. The evaluation could result in continued monitoring, a label change, a formal epidemiological evaluation or regulatory action.

Regulatory activities to monitor product safety
The World Health Organization (WHO) (using VigiBase), FDA (using AERS and VAERS) and EMA (using EudraVigilance) proactively monitor their databases to determine whether there are new risks associated with the use of a medicinal product or whether risks have changed. The safety signals that are identified have to be evaluated and characterized by biopharmaceutical companies. The FDA also conducts active surveillance using electronic databases.

The Sentinel Initiative and the Observational Medical Outcomes Partnership (OMOP): a national strategy for monitoring medical product safety
The Food and Drug Administration Amendments Act (FDAAA) of 2007 required FDA to collaborate with public, academic and private entities to develop methods for obtaining access to disparate health data sources and to validate means of linking and analyzing healthcare safety data from multiple sources. In response to this mandate, FDA announced in 2008 the creation of the Sentinel Initiative [FDA, 2011c], a long-term effort to create a national electronic system for actively monitoring the safety of FDA regulated medical products. Major activities of the Sentinel Initiative are the Mini-Sentinel Pilot to query privately held automated healthcare data and the Federal Partners Collaboration (FPC) to query publicly held automated healthcare data in the Centers for Medicare and Medicaid Services, the Department of Veterans Affairs and the Department of Defense. At the same time, the Foundation for the National Institutes for Health established the Observational Medical Outcomes Partnership (OMOP) consisting of representatives from FDA, academia, owners of different databases and the pharmaceutical industries [OMOP, 2009]. The purpose of OMOP is to develop and test scientific methods that could be used to analyze existing healthcare databases to identify and evaluate safety and benefit issues of drugs already on the market [Stang et al. 2010].

The Mini-Sentinel Pilot is a smaller working version of the future Sentinel System and it is a collaborative, active surveillance system that uses privately held healthcare data including administrative claims databases, pharmacy dispensing data and electronic health records. There are currently 26 collaborating partner organizations, known collectively as the Mini-Sentinel Collaborating Institutions, which provide access to healthcare data and to scientific, technical, methodological and organizational expertise. Mini-Sentinel works by creating a Coordinating Center, established by Harvard Pilgrim Health Care, Inc., which integrates the activities of the Collaborating Institutions by using a distributed data approach that enables healthcare data to remain in their local environment under the control of the participating partners. The advantages of this approach are that it maintains patient privacy by keeping directly identifiable patient information behind local firewalls in its existing protected environment and enables the owners of the database, who are familiar with its characteristics, to better analyze and interpret the results. This approach requires participating partners to transform their local data into a standardized format, which becomes part of the Mini-Sentinel Distributed Database. The Coordinating Center writes a single program for a given safety question, which each participating partner performs on its standardized dataset. The use of a common analytical program should minimize the potential for differences in results across different databases. The FPC is different than the Mini-Sentinel...
System in that it does not require participating organizations to transform their data into a standardized format. Instead, it develops a common active surveillance protocol and then each federal partner writes its own program to run the protocol on its database.

The Sentinel system can be used to proactively monitor adverse experiences in individuals taking a certain medicinal product, to identify a comparable cohort of individuals not taking the medicinal product of concern, and for drug utilization studies. Furthermore, it can be used for signal generation, signal refinement and signal evaluation. The methodology for conducting these studies is being developed and tested by OMOP. As of 12 December 2011, the Mini-Sentinel Distributed Database was composed of quality checked data held by 17 partner organizations involving 126 million individuals, with 43 million individuals currently enrolled accumulating new data and 27 million individuals with over 3 years of data, for a total of 345 million person-years of observation time from 2000 to 2011. It also contains data on 2.4 billion unique encounters including 40 million acute inpatient stays, 3 billion dispensing, and laboratory data on 12.6 million members with at least one laboratory result [FDA, 2011b].

Current projects being carried out within Mini-Sentinel Pilot include the development of a protocol for active surveillance of acute myocardial infarction (AMI) in users of a recently approved oral antidiabetic medication and a number of systematic reviews of the validity of algorithms using administrative and claims data for identifying a variety of outcomes such as transfusion-related sepsis, suicide or suicidal ideation, anaphylaxis (including anaphylactic shock and angioneurotic edema), lymphoma and pancreatitis. These activities of the Mini-Sentinel are described in detail in a special supplement of *Pharmacoepidemiology and Drug Safety* [Platt and Caranhan, 2001]. OMOP has conducted a series of experiments to generate empirical evidence about the performance of observational analysis methods in their ability to identify true risks of medical products and discriminate from false findings. The results of OMOP 2012 research are available online [OMOP, 2012].

**Box 1. New postauthorization regulatory requirements in the European Union.**

- Establishes the Pharmacovigilance Risk Assessment Committee: responsible for monitoring the effectiveness of all aspects of pharmacovigilance and for making recommendations to the Committee for Human Medicinal Products (CHMP).
- Periodic Safety Update Report, Sections 16, 17 and 18: required to perform a benefit–risk analysis at defined time periods.
- Risk Management Plan, Part IV: discuss the need for postauthorization long-term and real-world efficacy studies.

Regulation (EU) No 1235/2010 established the Pharmacovigilance Risk Assessment Committee (PRAC), which is responsible for making recommendations to the Committee for Human Medicinal Products (CHMP) on all questions relating to pharmacovigilance, risk management systems and their effectiveness, and on changes to the marketing authorization of the product. PRAC, which replaced the Pharmacovigilance Working Party, is responsible for monitoring the effectiveness of pharmacovigilance systems, for evaluating risk management and risk minimization programs, for approvals and updates to the risk management plan, for conducting signal detection on the EudraVigilance database, for conducting a benefit-risk analysis on certain products, and for the design and evaluation of Post-Authorization Safety Studies (PASS) [HMA and EMEA, 2012d].

**European Union legislation on pharmacovigilance**

Directive 2010/84/EU and Regulation (EU) No 1235/2010 on pharmacovigilance (European Parliament and Council of the European Union, 2010a, 2010b) have given EMA new authority to monitor product safety in the postauthorization environment. This legislation is the biggest change to the regulation of human medicines in the European Union (EU) since 1995 and has significant implications for applicants and holders of EU marketing authorizations. It sets out clearly identified responsibilities for EMA, Member States and pharmaceutical companies, which had to be adopted by July 2012. The important changes for pharmacovigilance in the EU are summarized in Box 1.

**Periodic safety update report and periodic benefit-risk evaluation report**

EMA and FDA require biopharmaceutical companies to prepare routine safety update reports on
all new products describing adverse events that have been reported during a specified time period. The Periodic Safety Update Report (PSUR) is now called the Periodic Benefit-Risk Evaluation Report (PBRER) and is required by the EMA [HMA and EMA, 2012c] and is proposed by the FDA [FDA, 2012]. PBRER is based on the International Conference on Harmonization (ICH) E2C (R2) guideline [ICH, 2012].

The purpose of these reports is to periodically perform an overall safety evaluation of a product to determine whether there has been any change in its safety profile since it was last evaluated. The PBRER contains a summary of any new safety issues identified during the reporting period, an estimate of the population exposed to the product, a summary of the marketing authorization status of the product, a list of the changes made to the package circular during the reporting period and summary analyses of specific adverse events. In addition, current requirements for the PBRER call for pharmaceutical companies to evaluate, on an ongoing basis, the benefits and risks of medicinal products in actual and/or long-term use, and to confirm that the benefit–risk profile remains favorable.

Risk management plans, and risk evaluation and mitigation strategies

The risk management plan (RMP) and risk evaluation and mitigation strategies (REMS) prepared prior to marketing authorization (discussed in the companion paper [Dieck and Sharrar, 2013]) will need to be evaluated and updated on a periodic basis once the drug is approved. The new EMA guidance on RMPs [HMA and EMEA, 2012b] has a section (Part IV) which discusses the need for postauthorization long-term and real world efficacy studies for certain medicinal products that have a pediatric indication, for advanced therapy medicinal products, for products where there are concerns about efficacy which can only be resolved after the product has been marketed, or when knowledge about the disease or the clinical methodology used to investigate efficacy indicates that previous efficacy evaluations may need significant revisions. This section should include a summary of the efficacy of the product, describing the studies and endpoints it was based on and the robustness of those endpoints. The need for further postauthorization studies to evaluate efficacy data for all patients in the target population should be discussed.

Postapproval observational safety studies resulting from risks identified postapproval

Although the need for an observational study can often be determined before approval, not all risks can be identified in the preapproval time period. Some observational studies may be undertaken in response to a safety issue identified in the postapproval time period. Many of these studies are carried out at the request of a regulatory agency, although manufacturers always have the option of initiating such studies on their own. One study requested by regulators is the PDE5 Inhibitor Use and Nonarteritic Anterior Ischemic Optic Neuropathy (NAION) study [ClinicalTrials.gov identifier: NCT00867815]. This study, which has a case-cross-over design and is scheduled for completion in 2015, examines whether the phosphodiesterase type 5 (PDE5) inhibitors, vardenafil, sildenafil or tadalafil, increase the risk for the development of NAION. Regulatory agencies became concerned after postmarketing reports of NAION were received after the products were marketed. Another study is the TYSABRI® Global Observational Program in Safety (TYGRIS) [ClinicalTrials.gov identifier: NCT00477113], which is a cohort study scheduled to be completed in 2014, and examines the incidence and pattern of serious infections, malignancies and other serious adverse events (SAEs) in Tysabri-treated patients with multiple sclerosis.

Conclusion

It is clear that the discipline of pharmacovigilance has changed dramatically over the past 10 years and it will undoubtedly continue to evolve in the years to come. Regulatory agencies expect biopharmaceutical companies to be proactive in identifying new safety issues, to focus on those important risks identified in drug development or in the postmarketing environment, to develop and implement effective risk mitigation strategies, and to be transparent in all activities relating to product safety. Pharmacovigilance activities will change as new methodologies are developed to monitor product safety using large electronic databases containing electronic health records. Since these changes will require more studies and more resources, pharmacovigilance activities should be based on sound scientific and epidemiological principles so that the data collected can be properly interpreted. Poorly designed studies or invalidated methods would only cause more confusion in an area where clarity is needed.
The future of pharmacovigilance is very exciting and positive. With advances being made in pharmacogenomics, it will be possible to identify individuals at high risk of experiencing an adverse event and preventing it from happening by not administering the drug. With advances being made in the use of electronic medical records and large databases, and enhanced epidemiological and statistical methodologies, it will be possible to identify safety issues earlier than in the past. As we learn more about risk communication, we should be able to improve our risk mitigation strategies so that the benefits of a medicinal product truly outweigh its risks.

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Conflict of interest statement
R.G.S. was employed by Merck & Co., Inc. from 1991 to 2008. G.S.D. was employed by Pfizer Inc. from 1986 to 2010.

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