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Product safety takes centre stage

Numerous initiatives in the US and Europe show that the focus on medical product safety is at its prime. All healthcare stakeholders are looking towards regulators and thought leaders to determine what the immediate and residual effects will be, writes Dr Richard Gliklich

Signed into law in September 2007, the US FDA Amendments Act (FDAAA) incorporated several key elements of drug safety, including the reauthorisation of the Prescription Drug User Fee Act (PDUFA), the Sentinel Initiative and the risk management requirements revision in Risk Evaluation and Mitigation Strategies (REMS).

The PDUFA was originally aimed at getting quality products to market more quickly by increasing the resources devoted to reviewing drug product applications. Over the years, it has been expanded to focus more on managing risks after approval. The most recent version includes a significant increase in post-approval focus, including additional resources for adopting new scientific approaches to drug safety, reducing the risk of medication errors, improving the utility of existing tools for detection and prevention of adverse events, and incorporating the new approaches into the FDA's drug safety programme.

Included in the PDUFA reauthorisation were commitments to:

- Develop and periodically update a five-year drug safety plan (the first version was released in December 2008);
- Assess current and new methodologies to collect adverse event information at various points through the product life cycle;
- Identify epidemiology best practices and develop guidance describing these practices (draft guidance is to be published by the end of FY 2010);
- Expand database acquisition to be used for targeted post-marketing surveillance and epidemiology;
- Develop and validate risk management and risk communication tools; and
- Improve post-market IT systems.

Sentinel

The Sentinel Initiative was launched last May, representing a major advance in the move from reactive adverse event reporting

to proactive surveillance. It is a national strategy and active surveillance system for monitoring medical product safety. It involves a public-private collaboration to use existing large electronic claims and medical records data sources maintained by private and government entities. In the past, the FDA relied primarily on:

- Health professionals or patients to submit an adverse event report to the manufacturer or the FDA;
- Case reports published in medical literature; and
- Results of post-approval and other clinical studies when they were performed.

The Sentinel Initiative is intended to provide the FDA with more powerful tools that allow ongoing surveillance and with the ability to query a broad array of information to identify possible adverse events. The initiative currently has eight contracts in process.

One Sentinel collaboration is with the Centers for Medicare & Medicaid Services (CMS). CMS Medicare Part D generates approximately one billion claims per year on medications used by more than 25 million beneficiaries. By linking data on prescription drug use to other Medicare claims information (including diagnosis, medical treatments, hospitalisations and physician services), stakeholders, including the FDA, are to be provided with a powerful new tool to investigate potential drug safety problems and questions about health outcomes. Any researchers interested in using the Medicare Part D data can file a request through an approved Research Data Assistant Center (ResDAC). The request is then passed along to the CMS, which decides whether the requested data can support the research protocol and for the minimum data necessary.

Another group collaborating with the Sentinel Initiative is the eHealth Initiative. The eHealth Initiative Foundation's "Connecting for Drug Safety Collaboration"

is a public-private effort designed to test and evaluate the feasibility and value of using electronic health information to support post-approval surveillance and drug safety. The collaboration is testing and evaluating safety signals using clinical data from electronic health records and other clinical systems and administrative claims data for a set of three "use cases" (Partners Healthcare, Regenstrief Institute, and the Department of Defense), including possible liver side-effects related to the use of cholesterol-lowering drugs, bleeding medications, or "designated medical events" (DMEs). Results are scheduled to be released this year.

A third Sentinel Initiative collaboration is with Outcome Sciences. This collaboration is dedicated to combining already existing US orthopaedic device implant registries to provide a comprehensive network and ongoing set of safety data on such implants. This registry network will also serve to provide broadly representative data on long-term outcomes of these procedures.

The FDAAA also authorises the FDA to require sponsors to develop and implement REMS for a drug at the time of approval or at any point during its lifespan. The statute provides that the FDA may determine that a REMS is necessary "to ensure that the benefits of the drug outweigh the risks of the drug". The law specifically states that REMS must consider how to manage risk without unduly burdening patients, particularly those with serious or life threatening diseases or with limited access to healthcare. The legislation also aims to improve data collection on adverse events by enabling the FDA to require post-approval studies or trials focused on safety, and it augments the FDA's power to require labelling changes or communications plans.

European moves

Like the FDA, the European Commission, in consultation with the EMEA, EU member states and interested parties, has also been taking steps to improve drug safety and risk

management efforts. Last September, the Commission revised its pharmacovigilance requirements in Volume 9A of "The Rules Governing Medicinal Products in the European Union." Volume 9A provides further guidance on risk management plans in Europe (EU-RMPs), including the conduct of post-authorisation safety studies (PASS).

An EU-RMP can be required by the authorities at any time during a product's life cycle and must include two parts:

- Part 1 encompasses a safety specification (a summary of the identified risks, potential risks, important missing information, and the populations at risk; it is considered an important element in determining the risk/benefit balance post-approval) and a pharmacovigilance plan;
- Part 2 includes an evaluation of the need for risk-minimisation activities and, if such activities are needed, then a risk minimisation plan.

An EU-RMP can be required for the authorisation of a product containing a new active substance, a biosimilar product, and a hybrid or generic product where a safety concern has prompted the need for a risk minimisation plan. Other situations requiring an EU-RMP are applications for a medical product for paediatric use; applications involving a significant change from the original marketing authorisation, such as a new dose form or a change in indication; and when a sponsor identifies a safety concern at any point during the product's life cycle. Volume 9A provides examples of recommended risk management methods, including restricted-access programmes and patient registries.

Volume 9A also requires all sponsors to submit Periodic Safety Update Reports (PSUR) once a product has received approval (even if it is not yet marketed). A PSUR must include a summary of new and changing safety information that becomes available during the period covered by the PSUR.

A PSUR is required every six months before marketing and during the initial two years of marketing; reports are then required annually for the subsequent two years, and every three years thereafter. However, the competent authority (ie, national authorities) or the EMEA can require a PSUR at any time following approval and can require the sponsor to provide more frequent updates if it considers them necessary. The legislation also provides the EMEA and the competent authorities of the EU member states with the authority to require post-authorisation safety studies (PASS) at the time of approval or at any point after approval when a safety concern needs to be addressed.

PASS may be required for identifying previously unrecognised safety concerns, investigating potential and identified risks, confirming the safety profile under normal use, and quantifying adverse reactions. Included in this section of the legislation are recommendations for study designs, including comparative observational studies (eg, cohort, case-control, cross-sectional studies), patient registries and randomised clinical trials.

ERMS initiatives

Outside of the Volume 9A regulation, the EMEA has been conducting other efforts to promote risk management and safety initiatives. In November 2007, the EMEA and the Heads of Medicines Agencies (HMA) agreed on a new two-year programme to further develop the European Risk Management Strategy (ERMS) initiatives. The primary goal of the 2008-09 programme is to implement a more proactive approach to risk management that encompasses the entire lifespan of a drug. This programme emphasises enhancing communication about drug risks, increasing the use of technology to monitor adverse drug events, improving the science of drug safety, and broadening the use of formal EU-RMPs.

As part of the ERMS initiatives, the EMEA launched the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) project, aimed at strengthening the monitoring of post-marketed medical products in Europe. ENCePP is not intended to replace any of the other pharmacovigilance tools and initiatives already existing, but to complement them. The project's goals include facilitating multi-centre, independent, PASS and studies focusing on a lack of efficacy.

Completed early this year, the first phase of ENCePP was to identify experienced pharmacoepidemiology and pharmacovigilance research centres across Europe. These 85 newly identified research centres will serve as a major resource for enabling the commission and implementation of PASS by healthcare stakeholders, such as the life sciences industry or regulatory agencies, that may provide further insight into the benefit/risk balance of marketed products in Europe.

observational studies

A key thread evident in all of the aforementioned regulations and initiatives, and necessary to help ensure the success of these programmes, is the increased use of observational studies, including patient registries. Unlike clinical trials, observational research provides data on how marketed products are actually being used in the real world without the restrictions of a controlled environment.

Registries not only provide insight into how the product is actually being prescribed by the physician or used by the patient, but because they can be conducted for much lower costs, they can extend over long periods of time. Additionally, since the treatment is not dictated by a study protocol, vulnerable populations who are usually excluded from clinical trials can be studied in the observational setting of a registry.

Observational studies also provide an ideal medium for active surveillance. They can provide systematic data on adverse events and the incidence frequency of these events. As mentioned, the FDA and the EMEA are looking at connecting data from registries already in process or, in some cases, providing the resources necessary to implement these studies, to connect the dots more quickly and easily on any potential safety issues that may be overlooked otherwise.

Also, as more risk management and safety studies are required for approval and become an integral part of active surveillance efforts, the quality of data generated from these studies is going to be more closely monitored and high-quality programmes expected. Efforts to create and promote best practices for conducting observational research are under way by some leaders in this field.

Through the recent regulatory initiatives, including the FDAAA in the US and Volume 9A in Europe, several key themes have emerged:

- The question of how safe is actually safe and how the risk/benefit equation can be more carefully managed;
- More real-world data are needed on larger populations and over longer periods of time;
- There will be a greater move from reactive and voluntary reporting to proactive and mandatory reporting;
- Improvements are needed in methods and technologies to identify more quickly and effectively who is at risk for which medications post-approval; and
- To meet all of the aforementioned, there will be an even greater turn towards observational methods and the development of best practices to ensure high-quality programmes.

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