



New directions in monitoring post-approval drug safety

The monitoring of drug safety after approval is a matter of increasing governmental and public concern. As Drs **Kelly Davis** and **Annette Stemhagen** report, the appearance of two new initiatives, Europe's ENCePP and the FDA's Sentinel Initiative, promises to significantly improve the process using a more modern, collaborative approach to the gathering and analysis of product safety information

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In both Europe and the US, a heightened focus on drug safety and risk management has led to new regulations that will result in significant changes for the pharmaceutical industry, particularly during the post-approval phase of drug development. Regulators at both the European Medicines Agency (EMA) and the Food and Drug Administration (FDA) have embarked on new initiatives to update and expand methodologies used to monitor product safety after approval. Each Agency is looking to both the public and private sectors to identify new sources of product safety information. Two new programmes are underway to gather post-approval safety data: the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) created by EMA and the Sentinel Initiative launched by the FDA. The strengthened emphasis on safety has also led both agencies to require industry to develop new risk minimisation strategies when important safety issues are identified prior to or after marketing.

The ENCePP

The EMA, in addition to its role in the scientific evaluation of new drug and biologic applications, has legal responsibility for management and coordination of pharmacovigilance activities across the European Union (EU). This task has expanded significantly in both scope and complexity since 2004, with the enlargement of the EU and near doubling of the number of member states. As a component of the strategy outlined in the EMA's Road Map to 2010¹ and the European Risk Management Strategy (ERMS)², the EMA is directing the formation of the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP). The purpose of the network is to have an established system of centres, both public and private, to facilitate collection and analysis of reliable pharmacoepidemiologic data. The ENCePP will proactively design and plan for pan-European pharmacovigilance programmes to



help answer unresolved safety questions that exist at the time of marketing authorisation, or address new concerns that arise after a product is marketed. The functions of the ENCePP will be to help strengthen the monitoring of medicinal products after approval through the conduct of post-authorisation safety studies, and to supplement programmes already in place such as EudraVigilance.

Currently, the initiative is being overseen by the ENCePP Implementation Advisory Group, which has 11 members from the EMEA, Committee for Medicinal Products for Human Use (CHMP), The Pharmacovigilance Working Party, Heads of Medicines Agencies from individual member states, representatives from international pharmacovigilance and pharmacoepidemiology organisations, and other experts in relevant fields. This advisory group will define the overall objectives of the programme and decide on the main operational activities of the network before handing over the leadership of the initiative to a steering group that will oversee implementation of the programme.

Four working groups have been tasked with developing major aspects of the ENCePP. One of the groups is focused on creating an inventory of existing independent research centres and institutions from across the EU with expertise in pharmacoepidemiology and pharmacovigilance. Another group is producing a similar inventory of pertinent databases, registries, and other data sources from across the EU member states. The other two working groups are formulating research standards and guidelines for the ENCePP and policies on transparency and independence.

ENCePP will be designed to allow researchers across the EU to work together on harmonising collection and analysis of pharmacoepidemiological data. Even though the ENCePP is a new group, it is well on its way to creating a better platform for post-approval product safety research across the EU.

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The Sentinel Initiative in the US

The Sentinel Initiative, launched in May 2008, is seeking to create or maximise the usefulness of automated databases for post-approval safety surveillance. The Initiative was legislated by the Food and Drug Amendments Act of 2007 (FDAAA, Section 905), which was signed into law in September 2007. Specifically, the Sentinel Initiative will compile pharmacoepidemiological data through electronic medical health records (EMRs) and medical claims databases. Through the power of this aggregation of databases, researchers will be able to conduct active surveillance and other post-approval safety studies, pulling together large amounts of data about product safety.

In addition, the Sentinel Initiative will redesign several existing post-approval safety databases that are already being used to monitor product safety. For instance, a new system called MedWatch Plus will replace the existing MedWatch system, a voluntary reporting system for adverse events (AEs) and serious adverse events (SAEs). MedWatch Plus will be used to report suspected adverse events associated with any FDA-regulated product. The distinction is that the current system is based on

voluntary reporting via disparate systems, while the new system will be fully electronic and fully integrated. With MedWatch, for instance, AEs are submitted via multiple channels (eg, manufacturers, health care professionals, and consumers) using a variety of computer programs, without a coordinated method to efficiently use the latest signal detection technology to identify potentially critical information within this mass of data. In contrast, MedWatch Plus will create a completely automated system using standardised data collection processes that will result in greater consistency, more timely reporting, easier data sharing, and, therefore, the ability to review aggregate data more efficiently.

To make MedWatch Plus as robust as possible, the FDA will also be collaborating with the University Health Systems Consortium (UHC) and the Patient Safety Net (PSN) database to promote reporting of SAEs. In addition, FDA is partnering with the Veterans Health Administration, the Department of Defense, the Centers for Disease Control and Prevention, the Center for Medicaid and Medicare Services, and the Massachusetts Institute of Technology to incorporate patient safety databases.


FDA holds public meetings on the progress of the Sentinel Initiative regularly, with the last public meeting (as of writing) held on December 16, 2008. Speakers at the workshop – including Dr Janet Woodcock, director of the FDA Center for Drug Evaluation and Research and Dr Mark McClellan, director of the Engelberg Center for Healthcare Reform at the Brookings Institution – discussed the status of the programme to date. The goals for the Sentinel Initiative, mandated under FDAAA, are aggressive and aim to access data from 25 million patients by July 2010 and from 100 million patients by July 2012.

Moving towards modernisation

In this era of increasing public concern over product safety, both the Sentinel Initiative and ENCePP strive to modernise the approach to monitoring post-approval product safety. In addition, both programs will take advantage of vast databases of health information with the goal of detecting early signs of emerging safety signals. It appears that the ENCePP will take a broader approach, however, as it is working in parallel to establish a network of research centres experienced in performing prospective pharmacoepidemiologic studies. The Sentinel Initiative will rely on retrospective data exclusively, gathered from EMRs and automated databases.

The FDA and the EMEA are moving towards a more collaborative approach to product safety, with participation from the regulatory agencies, industry, and academia in Sentinel and ENCePP. Acknowledging that transparency to the public is an important goal, the two programmes have also been actively engaging in regular publication and posting of meeting documents, public meetings, and workshops. Plans are in development to allow public

access to methodology and data when they become available. Regular inter-agency communications are also planned, with best practices to be shared around these two initiatives. Eventually it may be possible for data resources and output from one continent to be used effectively by the other to evaluate and examine specific safety issues. Similarly, the two perspectives might one day join forces to tackle common problems, thereby providing corroboration of specific risks and risk factors.

The new initiatives at both the FDA and the EMEA will result in a more highly structured and proactive system of collecting safety data to aid in the evaluation of products already on the market. Once these systems are in place – using the latest technology to link data sets and creating the opportunity for more stringent monitoring of post-approval data – the public's perception of the pharmaceutical industry and the agencies that regulate them will likely improve. It will be critically important, however, to be sure that good pharmacoepidemiology practices are employed. Involvement of scientists with a strong understanding of both the strengths and limitations of automated databases and observational data (eg, misclassification, channelling bias, confounding by indication) is essential to ensure appropriate study design and analysis so that incorrect or premature conclusions are not driving decisions about product safety. It is also imperative that industry maintain a seat at the table in all of these new initiatives – it is not sufficient for government and academia alone to forge new approaches. The talent, expertise and product-specific knowledge that exist within the pharmaceutical and biotechnology industry should be included in order to create the most effective plan for ensuring product safety. 

References

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2. (<http://www.emea.europa.eu/pdfs/human/phv/16895407en.pdf>).

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