Prepare for the long haul of drug monitoring

Richard Gliklich

As concerns have emerged in recent years over medications such as Vioxx and now Avandia, the need to improve the surveillance of approved drugs has become increasingly apparent. To ensure the success of the drugs they develop, biomedical researchers should track a wider set of clinical endpoints in drug trials and prepare to distinguish between real and false risks suggested by long-term safety monitoring.

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The process of drug safety monitoring does not end when a medication hits pharmacy shelves. This reality made headlines with the withdrawal of Vioxx in 2004 and the recent debate over Avandia. However, over the past decade, the existing post-approval surveillance systems in countries such as the US have increasingly been viewed as insufficient to identify potential safety problems in drugs and devices on the market.

This recognition has prompted regulatory changes, including those found in the Food and Drug Administration (FDA) Amendments Act of 2007, which gives the US agency the authority to require clinical trials of approved drugs. In addition, overseers have rolled out new safety monitoring methods that focus on improving both the collection and the reporting of data after approval. This may provide information on adverse events not seen in clinical trials, or events that occur in patients who are different (perhaps older or with more co-morbidities) than those typically included in clinical trials.

Some new programs attempt to streamline the reporting of adverse events; for example, the ASTER (ADE Spontaneous Triggered Event Reporting) Pilot Project launched in December 2008 enables doctors to download data from already established electronic health records and directly submit safety reports to the FDA without having to complete tedious paperwork by hand. Meanwhile, the national Sentinel Initiative, also initiated in 2008, monitors adverse reactions among drug recipients on Medicare[1].

New data sources include required post-approval studies, such as those that are conducted as part of Risk Evaluation and Mitigation Strategies. But they also include databases designed for other purposes, such as those originally designed for insurance claims, registries and electronic health records.

The development of post-approval surveillance systems raises questions about how they should function, what data should be included and how findings from the systems should be used. More research and pilot testing are needed to answer many of these questions, but it is already clear that the new systems must be broad—meaning that they gather data from a large, diverse patient population and from multiple types of providers—and they must use valid data. This means that researchers need to evaluate data sources to ensure that the information is collected in a systematic, standardized way. In addition, the ability to go back to the data source and validate specific outcomes will be essential when a potential safety signal is identified.

From a biomedical researcher's perspective, these changes to drug safety monitoring raise two important issues. First, the likelihood that a product will both attain approval and, eventually, retain approval will be driven by regulators' ongoing evaluation of the benefit-to-risk ratio. This means that companies will need to thoroughly understand the background safety signals for the disease area in which their products will be launched.

For products with a less-than-perfect safety profile, the 'benefit' aspect of the benefit-to-risk ratio may become the crucial piece in obtaining or retaining approval. Products with a fixed 'risk' aspect may be able to improve their ratio by showing increased benefit on the basis of secondary endpoints. Biomedical researchers will therefore need to consider a wider range of endpoints during drug development and certainly at the time of approval, to increase the 'benefit' side of the equation.

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Second, with efforts such as the Sentinel Initiative, governments and third parties are constructing large data sets, primarily using administrative data, to search for potential signals that a product is producing harm. Although well intentioned, these efforts will in some cases generate false positives, and rigorous studies will be necessary to prove or disprove these findings.

The problem is that major damage to a product's reputation may be done long before a new study is completed. Therefore, biomedical researchers will increasingly need to study the safety of their products from the later phases of development through product launch. These longer studies will require the use of tools such as patient registries, so that scientists will have high-quality data readily available to address any concerns raised from data mining efforts.

Whereas traditional biomedical researchers might assume that a clinical trial is the ultimate tool to study safety, as noted in a recent US Institute of Medicine report, "some observational studies of safety may have distinct advantages over trials," including being larger and more diverse and involving longer follow-up[1].

The changes to post-approval surveillance are still in the early phases, and it remains unclear what the final systems will look like. It is clear, however, that it will behoove companies to have data on hand after approval to address safety concerns. Biomedical researchers for their part should anticipate the new realities of post-approval surveillance and prepare for the long haul of studying drugs' benefits and risks.

Richard Gliklich is a professor at Harvard Medical School in Boston and president of Outcome Sciences, a medical patient registry firm based in Cambridge, Massachusetts.

1. Committee on Ethical and Scientific Issues in Studying the Safety of Approved Drugs; Institute of Medicine. Ethical Issues in Studying the Safety of Approved Drugs: A Letter Report. (The National Academies, 2010).

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