NEWS FEATURE

Anticipating REMS

The US FDA can now require companies to develop a risk evaluation and mitigation strategy (REMS) for therapeutic products. Bethan Hughes investigates the recent evolution of risk-management strategies in drug development.

As part of the FDA Amendments Act 2007, the FDA was granted new powers intended to enhance drug safety, such as being able to require companies to develop risk evaluation and mitigation strategies (REMS) to ensure that the benefits of a drug continue to outweigh its risks following approval. Although experience since REMS came into effect in March is relatively limited, so far, it seems that there has not been too much cause for concern in industry about the new requirements.

"The early signals are that the REMS are not proving to be a major regulatory hurdle," says Alan Goldhammer, Deputy Vice President for regulatory affairs for the Pharmaceutical Research and Manufacturers of America, Washington DC, USA. Indeed, of the 14 approved REMS at the time of writing, 12 have simply required a medication guide (http://www.fda.gov/cder/drug/DrugSafety/REMS.htm). However, the other two — Entereg (alvimopan) and Nplate (romiplostin) — have required more comprehensive plans, incorporating components such as a communication plan and elements to assure safe use. A number of pending approvals may also shed more light on the role of REMS in the evolution of risk-management strategies.

Before REMS, the FDA released guidance on the development and use of risk minimization action plans (RiskMAPS) in March 2005. Although REMS are similar to RiskMAPS, according to an FDA spokesperson there are several important differences. First, the FDA can require sponsors to submit REMS, whereas previously, the authority to require RiskMAPS was more limited. Second, REMS are enforceable with civil money penalties.

Also during 2005, the European Medicines Agency provided guidance on risk-management plans (EU–RMP) that have to be submitted as part of a marketing authorization application dossier. Now that REMS can officially be enforced, companies hope that the requirements of both agencies will converge. "As a global organization we have to encompass the needs of both agencies and in an ideal world they would be similar," says Alastair Benbow, Senior Vice President of Medical Governance Management at GlaxoSmithKline (GSK), UK. As both agencies have agreed to cooperate in the area of risk management, this hope should be realized (*Nature Rev. Drug Discov.* 6, 589–590; 2007).

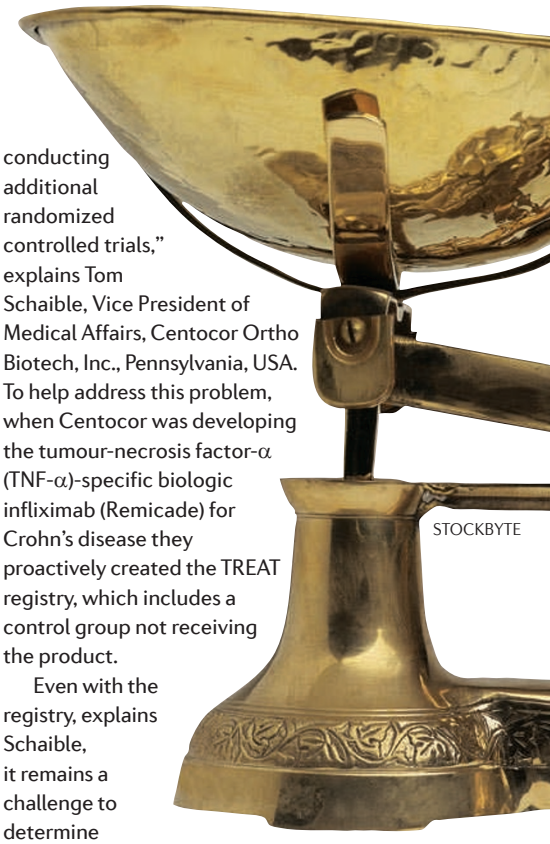
While REMS and EU–RMPs are formally applied at the time of product filing, they do affect drug development says Joanna Haas, Vice President, Pharmacovigilance, Genzyme Corporation, Massachusetts, USA. "If we need to have an active strategy for management at the time of marketing, we have to build it into our thinking during development."

Benbow agrees, "At GSK we put a benefit/risk management plan in our early development programmes so that from the first time in human we have a plan of all the things that we need to consider for our asset — such as signals from animal pharmacology and the structure of the molecule — to predict the side-effect profile and create a plan for mitigating known or suspected risks."

To help identify possible safety issues prior to clinical development, GSK developed an online signal management system called Molecular Clinical Safety Intelligence (MSCI) with an external group called the Lincoln Safety Group, Phase Forward, Massachusetts, USA. MCSI compares the chemical and pharmacological profiles of early drug candidates to safety knowledge about drugs that have been previously tested, which is helping GSK to reduce attrition. "We can help select the molecules that have the best chance of getting through to market with the best adverse-event profile," says Benbow. Other tools also help GSK identify safety signals during clinical development. "We are finding it increasingly useful in defining whether there is something that warrants further exploration," he adds.

Post-marketing pharmacovigilance data also feed prospectively into drug development. Databases, such as the electronic health record systems and medical claims databases being integrated for the FDA's Sentinel Initiative (http://www.fda.gov/oc/initiatives/advance/sentinel/), can be probed to help understand background adverse events experienced by a certain patient population, or provide safety information on use of similar products that have already been approved.

This strategy is not without its challenges, however. "Usually, in the post-marketing environment you don't have the luxury of conducting additional randomized controlled trials," explains Tom Schaible, Vice President of Medical Affairs, Centocor Ortho Biotech, Inc., Pennsylvania, USA. To help address this problem, when Centocor was developing the tumour-necrosis factor-α (TNF-α)-specific biologic infliximab (Remicade) for Crohn's disease they proactively created the TREAT registry, which includes a control group not receiving the product.



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Even with the registry, explains Schaible, it remains a challenge to determine whether an increased rate of infection or cancer is due to the agent. "Patients that are receiving our drug have more severe disease and have generally been exposed to other drugs that have other toxicity problems. These are confounding factors for assigning drug associations." Nonetheless, the registry and other post-marketing reports helped to identify the increased risk of reactivation of latent tuberculosis that is now well known for patients receiving an anti-TNF-α biologic. This knowledge was built into Centocor's recent clinical trials for the anti-TNF-α biologic golimumab, now in Phase III, for which patients were pre-screened with newer, more sensitive screening tests for latent tuberculosis.

Regardless of whether safety signals are identified during drug development or post-marketing pharmacovigilance, it is clear that REMS and EU–RMPs may be useful tools for managing risk. They may even help companies to develop products that have strong efficacy but known toxicities says Sara Radcliffe, Vice President for Science and Regulatory Affairs at the Biotechnology Industry Organization, Washington DC, USA.

"What regulatory authorities and companies really aim to accomplish is to identify the appropriate level of risk that is compatible with the benefit that the drug provides. That level of risk can be different from one drug to another based upon the benefit that the drug can provide. Not treating a disease appropriately is a risk in itself," concludes Schaible.