Managing Risks and Resources

Jill Wechsler

Risk is the key word at FDA these days. To encourage the safe and appropriate use of prescription drugs, the agency is promoting the concept of risk management. This involves an increased focus on how medications are prescribed and used in the real world and the design of preclinical, clinical, and product quality studies to provide requisite information. Rising interest in parenterals and gene therapies is focusing agency attention on quality standards for such complex treatments. At the same time, FDA may reduce manufacturing data requirements in applications for low-risk products as a way to streamline regulatory demands.

Although some FDA efforts to reduce medication errors may expand data requirements, other regulatory proposals could limit reporting requirements for low-risk products.

Manufacturers, however, are wary that risk management may translate into increased regulations and demands for more data, particularly in the clinical area. Some FDA reviewers are requesting additional clinical data and product testing to ensure safety more broadly. Recent proposals to revise professional labeling may be costly to implement, and emphasis on postapproval studies and oversight is increasing. If standards are set too high, manufacturers fear that bringing new products to market could become more difficult.

Promoting safe use

Underlying FDA's focus on risk management is the public outcry concerning several recent recalls and withdrawals of medicines from the market. Some FDA critics have charged that the agency is rushing through approvals of unsafe products that should never be allowed on the market. Janet Woodcock, director of FDA's Center for Drug Evaluation and Research (CDER), maintains that withdrawal rates today are similar to those of the past and supports efforts to bring new drugs to market quickly. But she also acknowledges that FDA's traditional methods for promoting the safe use of new drugs are not working. "Dear doctor" letters and black-box warnings on labels fail to prevent clinicians and patients from using drugs for contra-indicated uses, Woodcock said at a conference sponsored by the Drug Information Association (DIA) in April. Clinical trials for some products fail to predict important risks, and the idea that all FDA-approved drugs are safe is just not true, Woodcock explained. Some problems do not appear until thousands, if not millions, of people have tried a new therapy. Even so, she believes that it is time for FDA to take action to reduce preventable risks associated with prescription drugs.

While still in the information-gathering stage, Woodcock is implementing strategies to manage specific products that are medically important but carry added risks for patients. For example, FDA has negotiated a highly restricted access program for Thalidomide, a patient information program to prevent exposure of pregnant women to Accutane, and restricted distribution for Mifepristone. However, manufacturers have not agreed with every CDER risk management proposal — as seen in the decision by GlaxoSmithKline last fall to halt the marketing of its Lotronex irritable bowel syndrome therapy after several serious adverse events instead of accepting FDA's proposal for a highly limited distribution plan.

FDA launched a formal risk management effort two years ago with the release of a report on "Managing the Risks of Medical Product Use." A few months later (November 1999) the Institute of Medicine issued "To Err is Human: Building a Safer Health System," which made headlines with the claim that almost 100,000 Americans die each year because of medical errors — with medication errors a leading factor. In response, the federal Quality Interagency Coordination Task Force examined how government agencies could help reduce medical errors. FDA issued a report last February outlining the actions it was taking, many directly affecting manufacturing processes, to improve information about drugs and medical products.

Revise product labeling. After years of analysis, FDA published a proposed rule in December 2000 to overhaul the format and content of prescription drug labeling for health professionals. A key change is to add a highlights section at the beginning of the package insert (PI) to summarize

Jill Wechsler
is *Pharmaceutical Technology*'s Washington editor, 7715 Rocton Ave., Chevy Chase, MD 20815, tel. 301.656.4634, e-mail wexson@idsonline.com.

information that manufacturers and FDA consider most important for prescribers. The proposal reorganizes the PI information, adds an index, and uses icons to identify important features. Manufacturers, however, consider the labeling proposal overly detailed and fear that highlighting the most common adverse events may expose them to lawsuits for failing to warn patients equally of rare but harmful side effects. Industry and FDA microbiologists also oppose the idea of excluding certain in vitro data regarding microorganisms.

Moreover, manufacturers point out that adding the half-page highlights section and index, using larger type size, and providing additional information in a more spacious format will double the size of most PIs and make it difficult to squeeze the necessary information onto a one-page insert. Such changes will require retooling of packaging lines and entail significant expenditures — far beyond FDA's cost estimates. Comments filed by Merck indicate that equipment changes to produce larger inserts could cost ≤$700,000 per packaging line, and the bill to convert the company's more than 50 lines could reach $40 million.

The proposed rule also calls for revisions to the contents and format of package and container labels to make them easier to read. Although not so controversial, these provisions still would add to the cost of overhauling packaging systems.

Ultimately, an electronic system for disseminating labeling information may be the only efficient way to convey timely labeling information to prescribers and patients. Although FDA plans to move in that direction, electronic labeling is probably years away. FDA extended its period for public comment on the proposed rule until 22 June 2001, and revisions of the policy are expected to take many months. After that, manufacturers say they will need more than a year to implement any final policy.

Reduce confusion involving product names and packages. CDER's Office of Postmarketing Drug Risk Assessment reviewed approximately 300 proprietary names last year in an effort to avoid look-alike and sound-alike names and packages. FDA wants manufacturers to do more testing of proprietary names for new products to avoid confusion. The agency is drafting a guidance that will outline methods for testing proprietary names and is looking at packaging standards that may avoid dosing and product mix-ups.

A related initiative is to print machine-readable bar codes on medication packages. Many experts believe that adding standardized machine-readable codes to pharmaceutical packaging could reduce errors, but the effort has run into technical and policy difficulties. The National Coordinating Council for Medication Error Reporting and Prevention is preparing a white paper on this issue based on the discussions and recommendations that came from FDA and manufacturers while at a conference last August.

Expand adverse event reporting. FDA is developing a rule that requires manufacturers to file reports electronically into its Adverse Event Reporting System (AERS).

Manufacturers fear FDA is pursuing a zero-risk regulatory approach.

This would speed up the detection of safety problems, including information about product defects and hazards involving pharmaceutical manufacturing, labeling, and packaging. The electronic filing rule would mesh with a recently issued guidance, which implements standards adopted by the International Conference on Harmonization (ICH), on when and how manufacturers must file postmarketing reports on serious adverse experiences.

To prevent adverse events more effectively in the future, FDA wants to move beyond relying on manufacturers and health professionals to send in reports after the fact. One proposal is to include drugs and biologics in a pilot program for medical devices — the Medical Product Surveillance Network (MeDSuN) — that trains personnel in hospitals to report to FDA any injuries, deaths, and close calls associated with medical products.

Another strategy is to expand FDA access to databases that link pharmaceutical use to outcomes in population-based settings. FDA is evaluating ways to share data with other federal agencies and is working with Centers for Education and Research on Therapeutics that has links to large healthcare databases developed by HMOs, insurers, and state Medicaid agencies. Health and Human Services (HHS) Secretary Tommy Thompson recently formed a Patient Safety Task Force to integrate various HHS adverse event reporting systems so it can coordinate efforts to detect and deal with medical errors.

New quality concerns

These initiatives primarily involve efforts to improve the safe use of medications by expanding the scope of clinical trials and postmarketing surveillance, but they address the issue of product quality very little. In fact, Woodcock notes that although manufacturing defects have led to patient injuries in the past, FDA research, surveillance, and plant inspection programs have reduced manufacturing quality problems to a minimum. However, the emergence of genomics and individualized therapy is stimulating interest in new types of therapies and less common dosage forms, reviving questions about whether current regulatory policies address quality issues adequately.

A sign of this development was a recent workshop cosponsored by FDA and the American Association of Pharmaceutical Scientists (AAPS) to explore policy options for ensuring the quality and performance of sustained- and controlled-release parenterals. New developments in drug discovery are boosting interest in liposomes, gels, implants, and suspensions that can target the delivery of therapies to the body. These dosage forms may reduce adverse events and offer simpler dosing regimens that can improve compliance.

Despite such therapeutic advantages, manufacturers acknowledge that parenterals are complex formulations and present new challenges for ensuring the quality and performance of what are considered high-risk products, noted Helen Winkle, acting director of CDER's Office of Pharmaceutical Science. For example, liposomes raise particular formulation and safety issues because they carry a drug directly into the blood stream.

This group of experts from industry and FDA examined a range of issues, including the need for accelerated dissolution testing to assess shelf life, how to ensure lot-to-lot quality, how to devise in vitro release standards, and whether there are opportunities for in vitro–in vivo correlations. The overall aim of the workshop was to propose policies that will encourage manufacturers to build in quality procedures and not rely on after-the-fact oversight. The workshop leaders are trying to identify information gaps and where more research could address important issues. One goal is to decide which areas for further study could be explored by the Product Quality Research Institute.

Similarly, to enhance patient safety in gene therapy testing, FDA's Center for Biologics Evaluation and Research (CBER) may request information about manufacturing quality assurance and quality controls as part of investigational new drug submissions. Philip Noguchi, director of CBER's Cellular and Gene Therapies Division, recently suggested that CBER might put a clinical study on hold if the sponsor fails to provide documentation regarding manufacturing quality assurance. This proposal reflects concerns that gene therapy products can easily become contaminated during complex manufacturing processes, a situation that can be compounded by frequent outsourcing of production at early research phases. FDA wants data on cleaning procedures and says that tests for sterility, residual toxic reagents, endotoxins, concentration, and activity–gene expression should be performed for each lot that uses plasmids as intermediates.

Zero-risk strategy?

Despite the positive tone of Woodcock's risk management initiative, industry is leery that FDA's initiative reflects a shift to more restrictive policies. At the DIA conference last April, Bert Spilker, senior vice-president of the Pharmaceutical Research and Manufacturers of America, complained that FDA is erecting too-high hurdles to bringing new products to market. Spilker pointed to inconsistent study requirements across CDER review divisions such as requests for clinical studies with even more patients than in ICH guidelines, for comparative clinical trials, for post-hoc subgroup analysis of US studies in large multinational trials, and for assessment of additional metabolites in human clinical pharmacology studies.

Bruce Burlington, senior vice-president at Wyeth-Ayerst Pharmaceuticals (St. Davids, PA), agreed that manufacturers fear FDA is pursuing a zero-risk regulatory approach and called for policies based on evidence instead of theoretical concerns. To promote collaboration in devel-

oping risk strategies, Burlington suggested that FDA establish high-level committees to review risk management proposals.

FDA's response is that it is looking for opportunities to reduce data filing demands for drugs and manufacturers that carry less risk. The agency issued a guidance last August that outlined a biopharmaceutics classification system for immediate-release solid oral dosage forms based on product solubility, dissolution, and intestinal permeability. The objective is to establish a framework for identifying low-risk products based on these characteristics that would be eligible for waivers on some bioavailability and bioequivalence studies during product formulation as well as generic drug development. Similarly, last May an AAPS workshop on regulatory issues related to dissolution testing explored further options for using in vitro tests to replace some in vivo studies.

FDA also is reexamining its policies for cutting manufacturing data filing requirements related to postapproval changes. The agency issued a guidance in November 1999 outlining reporting policies for low- and high-risk changes, specifying that manufacturers do not have to obtain agency approval to implement certain minor production modifications. FDA is considering whether it should further curtail the chemistry, manufacturing, and controls data required in applications for low-risk new drugs and generic products.

These policy revisions aim to reduce FDA resources devoted to the oversight of relatively safe and low-risk products to focus on more difficult situations. In its budget request to Congress for fiscal year 2002 (begins 1 October 2001), FDA seeks an additional $5.5 million to support import and inspection programs and another $4.1 million to fund adverse event reporting and other patient safety activities. If approved, FDA says it will use the additional funds to conduct more inspections of domestic and foreign manufacturing sites, particularly those experiencing quality problems with nonuniform dosage units, cross-contamination, sterility, and product mixups. The agency also wants to increase inspections involving foreign-source active pharmaceutical ingredients to detect counterfeits, which has been a leading concern on Capitol Hill. Added funding also would expand surveillance of marketed drugs by enabling FDA to further refine the AERS program, allow MeDSuN to include drugs, increase links to broad-based health systems databases, and develop error reduction strategies with manufacturers and the medical community.

An extra $20 million for these initiatives and salary increases is not that much by Washington spending standards, but it is a welcome amount for FDA. In recent years, the agency has received virtually no budget increases in real terms and has been forced to shift funds from oversight and research activities to pay mandated salary hikes. After robbing Peter to pay Paul for a long time, FDA finally might be able to enhance efforts to ensure product safety while developing rational regulatory programs. **PT**