



Drug Safety Concerns Shape Manufacturing Policy

Jill Wechsler

FDA wants manufacturers to revise product labeling and packaging and step up adverse-event monitoring to reduce risky product use.

Risk management is in the spotlight at FDA as part of efforts to gain more control of how drugs are used. The agency is reorganizing its staff and developing new policies. The goal is to improve processes for evaluating risk factors in new drug candidates as well as track and evaluate adverse events once a product is on the market. These objectives have led the agency to revise requirements for packaging and overseeing foreign manufacturers and production activities, thus affecting pharmaceutical manufacturing.

CDER reorganization emphasizes safety

In recent months, FDA has taken several actions to expand its oversight of drug safety issues and enhance its ability to manage postmarketing activities. The most visible of FDA's actions is the establishment of the new Office of Pharmacoepidemiology and Statistical Science (OPSS) in the Center for Drug Evaluation and Research (CDER). The main component of this new office is the renamed Office of Drug Safety (ODS), formerly the Office of Postmarketing Drug Risk Assessment (OPDRA). Both OPDRA and CDER's Office of Biostatistics were shifted to OPSS from CDER's Office of Review Management (ORM), along with the agency's MedWatch program and patient labeling-risk communication functions.

ORM also has a new name — Office of New Drugs (OND). Its title reflects an increased focus on review and approval of new drug applications and supplements. OND now is headed by John Jenkins, who was selected as director in December. He works closely with the new safety office to evaluate risk concerns during the review process.

ODS manages these functions through the following three divisions:

- Drug Risk Evaluation. Julie Beitz leads a group of more than 40 people who detect and assess

reports of safety problems for all marketed drug products. The group works with OND medical reviewers to identify and evaluate the context of such safety concerns. In addition, 10 epidemiologists review the protocols for Phase IV studies and advise about postapproval risk-management strategies such as patient registries or restricted-distribution programs. The staff evaluates patient databases and published literature to estimate the effect safety problems may have on public health.

- Medication Errors and Technical Support (METS). Jerry Phillips is the acting director of METS as well as ODS's associate director. The METS staff analyzes medication errors involving drugs already on the market and reviews proprietary names and labeling of new drugs before market approval to reduce the potential for errors with medication use.
- Surveillance, Research, and Communication Support (SRCS). Under Anne Trontell's leadership, this new unit handles data resources, risk communication, and outcomes research related to drug safety risk-management programs. It assumes management of FDA's MedWatch program, previously conducted from a CDER staff office, and activities formerly handled by CDER's Division of Drug Marketing, Advertising, and Communications. These activities include the development of medication guides, patient-package inserts, and pharmacy information surveys. Another assignment is to provide an international regulatory liaison for postmarketing safety issues related to drugs and biologics. SRCS also manages FDA's use of drug safety and epidemiologic data resources, including CDER's Adverse Event Reporting System, drug use data from IMS Health, and access to insurance and health plan databases.

New leadership

Heading up OPSS is Paul Seligman, who came to CDER from the Department of Energy (DOE) in July 2001. Seligman was deputy assistant secretary for health studies at DOE, where he was involved

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with epidemiology and surveillance programs related to radiology and nuclear weapons. Seligman reports to CDER deputy director Steven Galson, another newcomer who came to FDA in April 2001 to oversee the expansion of drug safety activities. Formerly with the Environmental Protection Agency, Galson has been serving as CDER acting director while director Janet Woodcock is working temporarily in the FDA commissioner's office to develop the agency's counterbioterrorism plan.

One unanticipated task for Galson and Seligman will be to appoint a new director of ODS following the departure of Peter Honig, former head of OPDRA and briefly of the new drug safety office. Honig left FDA last month to direct a new risk-management office at Merck, a move reflecting that company's interest in emphasizing product safety and risk-management strategies. Honig's surprise departure from FDA comes at a critical time for the development of many agency risk-management issues.

CDER will gain added advice about drug safety issues from its new advisory committee for drug safety and risk management (see *Pharmaceutical Technology's* "Washington Report" column, February 2002). This new subcommittee to CDER's Advisory Committee for Pharmaceutical Science is scheduled to meet 23 April to review safety issues related to Glaxo-SmithKline's Lotronex (alosetron). Glaxo pulled the product off the market in November 2000 because of serious adverse events and a dispute with FDA about a suitable risk-management strategy. At the April meeting, Glaxo is expected to present safety data derived from Phase IV studies at the time of withdrawal. The session also will provide an opportunity to evaluate FDA risk-management proposals and safety strategies available to manufacturers.

Boosting bar codes

In addition to expanding agency staff and structure for overseeing drug safety issues, FDA is working on a number of policies and programs to enhance the safe use of drugs and reduce medication errors. One priority initiative is to develop a policy to increase bar coding on prescription-drug packaging. The agency's policy staff has

FDA registers foreign manufacturers

To improve its ability to contact a foreign manufacturer about a drug-related health or safety concern, FDA issued a final rule in November 2001 requiring all firms making products for the US market to register with the agency and designate a US-based agent. The new policy is designed to help track a drug product's foreign material source and improve scheduling of inspections for foreign manufacturing facilities.

The rule applies to all foreign organizations that produce or import drugs, biologics, or medical products for the US market. These entities must register the name and location of manufacturing establishments and list all drugs in commercial distribution in the United States. Foreign firms also must list the name of an agent based in the United States, a policy designed to improve communications between FDA and foreign establishments.

In the past, FDA required registration only of domestic manufacturers. Foreign firms were

encouraged to inform FDA of facility locations, but many failed to do so. The FDA Modernization Act of 1997 included a provision requiring registration of foreign manufacturers, partly in response to growing concerns about the quality of imported active pharmaceutical ingredients. As FDA developed its proposal to implement the new policy, foreign manufacturers and regulatory authorities raised objections to the scope of the rule and the requirement for a US-based agent. The Canadian government protested that the policy was costly and unfair to Canadian manufacturers. FDA decided that it could not treat Canadian firms differently and that its request for an establishment's address, names of owners, and identifying information was quite minimal. FDA also stuck to its demand that an agent has to be a person or company physically in the United States — not a mailbox or answering service.

been researching current bar code programs and how best to apply them to drugs. FDA described the bar code initia-

tive in its December 2001 semiannual regulatory agenda and hopes to issue a proposed rule this summer. Moreover, FDA

senior associate commissioner for policy Bill Hubbard included bar coding on his list of priority regulatory reform efforts in a January presentation to Health and Human Services secretary Tommy Thompson's new advisory panel about regulatory reform.

Pharmacists and medical personnel want manufacturers to expand bar coding to unit-of-use pharmaceutical packages so personnel can use computers and scanners to ensure that the right patient receives the right dose at the right time. FDA may decide to require all packages for drugs and biologics to include a bar code containing at least the product's national drug code numbers.

Also under consideration is whether to require a drug's expiration date and lot number in the bar code to identify expired or recalled products. Although this information is useful, FDA acknowledges that requiring more data increases production costs for manufacturers. The agency has considered a voluntary bar coding program but is concerned that manufacturers

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would either not participate or would adopt a variety of incompatible bar code formats. This outcome would do little to encourage hospitals to invest in scanners and computer equipment needed to scan the digitized information.

FDA's preliminary estimates are that a bar code rule will cost industry between \$500 million and \$1.4 billion over 10 years depending on the complexity of codes, the

range of products included, and the need for manufacturers to overhaul packaging operations. The fear is that broad requirements will prompt manufacturers to drop some types of packaging and supply some products only in bulk containers. Health professionals and safety experts prefer the convenience of unit-of-use packages, but these packages generally are more expensive for drug makers to produce. Hubbard

noted that his office expects to take six months just to do a more detailed economic analysis of a bar coding rule. A final regulation could take several years.

Curbing label and name confusion

FDA also is developing several new rules and policies to promote safe drug use by improving information to prescribers and patients. A priority initiative, designed to revise the content and format of professional labeling for drugs and biologics, has been in the works for several years (see *Pharmaceutical Technology's* "Washington Report" column, June 2001). Manufacturers are worried that the agency's proposal to update drug labeling will make written information in pharmaceutical package inserts much longer, requiring costly changes in manufacturing and packaging operations. An added concern is that listing important prescribing information in a highlighted section may make companies more vulnerable to liability charges. On the other hand, FDA officials believe that the new format will make it much easier for practitioners to understand important prescribing information and to ensure the safe use of medicines. To ease the transition to the new format, the agency initially may apply the requirements only to new products and permit manufacturers to phase in labeling requirements for previously approved drugs.

ODS also wants to reduce possible confusion from look-alike and sound-alike product names. To improve its ability to detect name problems, the division plans to develop guides about submitting proprietary drug names for agency evaluation. CDER is working on an internal policy to help reviewers evaluate trade names to prevent medication misuse. This policy may be facilitated by computer software designed to identify proposed proprietary names that may be similar to existing designations among the 15,000 drug trade names in the United States. ODS also plans to create standards for developing names, labeling, and packaging to avoid medication errors. A future policy about packaging, for example, may spell out the safety issues involved in a manufacturer's decision to use a certain type of packaging to ensure correct administration and to avoid overdoses. The ODS annual report, which was issued in January, also notes that FDA

may develop regulations to compel manufacturers to comply with standards for labels and packaging to ensure safe product use.

More collaboration

Merck's move to hire FDA's Honig as vice-president of risk management reflects an increased interest among manufacturers to give drug safety issues more promi-

nence. Officials at FDA and Pharmaceutical Research and Manufacturers of America have formed a risk-management committee to reach consensus about new approaches to drug safety problems. Agency officials have long lamented their limited regulatory authority to address safety concerns. FDA now only can call for changes in product labeling or require a manufacturer to send letters about safety

concerns to health professionals. However, CDER officials recognize that these tools often don't bring about changes in prescriptions or patient use of certain therapies. In those cases, the agency can require withdrawal of a medicine from the market but usually is reluctant to take such extreme action.

Instead, FDA tries to negotiate product-specific risk-management programs with individual manufacturers. For example, the agency worked with Roche to prevent the use of Accutane (isotretinoin) by pregnant women and with Actelion Pharmaceuticals to ensure liver monitoring for Tracleer (bosentan). To gain more options, ODS is planning to develop a risk-management toolbox that will provide a more systematic approach to selecting methods for managing risk and for assessing their effectiveness. The ultimate goal is to develop off-the-shelf systems that can be applied to all drugs that require risk management.

These issues will be part of continuing discussions about the scope and focus of the next phase of the Prescription Drug User Fee program, which is set for reauthorization by the end of September. CDER would like to have a portion of user-fee revenues available to support the expansion of adverse event reporting systems, prepare additional guidance documents about safety reforms, and develop new risk-management approaches. Manufacturers are wary of expanding user fees to fund more FDA activities but may consider added payments to support certain postapproval programs.

CDER plans to issue a risk-management white paper later this year to define current problems, describe ways to address risks, and outline future objectives. Some of the proposals described in this column may be components of a broader proposed rule about postmarketing drug-risk surveillance, which is expected later this year. All these initiatives put safety issues in the forefront of product development and distribution. **PT**