Promoting Quality in Drug Manufacturing

Jill Wechsler

Jill Wechsler is *Pharmaceutical Technology*'s Washington editor, 7715 Rocton Ave., Chevy Chase, MD 20815, tel. 301.656.4634, jwechsler@advanstar.com.

FDA is re-engineering the CMC review process for innovator and generic drugs and backing risk-based ICH quality standards.

As pharmaceutical manufacturing evolves from an art form to a science-based process, the Food and Drug Administration is eyeing opportunities to translate better information about product quality into more risk-based regulatory review and inspection policies. The overriding goal is to apply a "quality by design" approach to pharmaceutical manufacturing to achieve the "desired state" of product quality and performance, explains Ajaz Hussain, deputy director of the Office of Pharmaceutical Science (OPS) in FDA's Center for Drug Evaluation and Research (CDER). At the July meeting of FDA's Manufacturing Subcommittee of the Advisory Committee on Pharmaceutical Science, Hussain and others outlined a number of steps FDA is taking to encourage more rational pharmaceutical development and manufacturing systems.

If a manufacturer can demonstrate a good understanding of key product attributes (*e.g.*, stability, bioavailability) and provide evidence that it can control critical variables and detect product deviations, regulatory authorities will be able to review applications in one review cycle, permit improvements in a manufacturing process without prior approval, and implement a risk-based inspection process, explains Pfizer Vice-President John Berridge. To achieve this ideal situation, FDA is taking steps to re-engineer its chemistry, manufacturing, and controls (CMC) review process in new drug applications (NDAs) and abbreviated NDAs (ANDAs) for generic drugs. Prime goals are to curb multiple review cycles, reduce application resubmissions, and reduce oversight of most postapproval changes. At the same time, FDA is working with other regulatory authorities and manufacturers to reach agreement on new standards for submitting drug quality information in the common technical document (CTD) developed by the International Conference on Harmonization (ICH).

Streamlining CMC reviews

The current CMC review system is resource-intensive, imposes unnecessary regulatory burdens on industry, and discourages manufacturers from making improvements such as those achieved through process analytical technologies (PAT) in approved products, observed Moheb Nasr, director of CDER's Office of New Drug Chemistry (ONDC) in OPS. He cited a number of factors for this unfortunate state:

- ONDC reviewers evaluate all CMC information, regardless of its importance or the reviewer's expertise.
- Applications closely follow FDA and ICH guidances, even if a different manufacturing approach is more logical.
- ONDC does not examine manufacturing process information in detail because the current system leaves that task to FDA's field force.
- FDA and manufacturers seek tight product specifications determined by limited data to ensure consistency in a manufacturing process; this often leads to recalls and drug shortages.
- Manufacturers frequently submit late and voluminous CMC amendments, which delay reviews.
- NDAs seldom include critical information about pharmaceutical development which is necessary for a risk-based assessment of the product.
- CMC information in applications varies widely because many applicants fail to consult with FDA before filing an NDA, and fail to follow agency recommendations when sought.

These factors delay application approvals and discourage manufacturers from improving systems, adding to the cost of already expensive new drug products. A recent study found that manufacturing problems are responsible for delaying first-cycle NDA reviews of many new molecular entities. And with its workload rising, CDER is eager to eliminate unnecessary and redundant activities. This past year, ONDC reviewed 159 NDAs, 342 commercial investigational new drug applications (INDs), 1745 supplements, and more than 1000 annual reports.

A risk-based CMC review system, which is being developed first for conventional drugs, will focus on the relevance to safety and efficacy of critical quality attributes such as chemistry, formulation, manufacturing processes, dosage form, and product performance, Nasr explains. Interdisciplinary teams of chemists, pharmacists, engineers, and others using modern statistical methods to evaluate information in pharmaceutical development reports (PDRs) and a quality overall summary (QOS) will conduct reviews. The new approach aims to achieve more consistency among chemistry review teams and improve FDA's ability to oversee new technologies, combination products, and novel dosage forms.

FDA is implementing this more streamlined review approach first for CMC sections of resubmitted NDAs. Under a pilot study, a senior CMC reviewer will conduct a quick (14-day) preliminary assessment of a resubmission, order a copy of any referenced drug master file, and develop an "assessment protocol" for reaching approval. This information then will go to a primary reviewer who will perform an in-depth assessment and seek to resolve CMC issues quickly.

ONDC also is exploring ways to down-regulate or eliminate those CMC supplements unlikely to adversely affect the quality, purity, or stability of a drug product. A more efficient supplement review process would encourage continuous post-marketing product improvement by manufacturers and also free up ONDC resources for NDA reviews, Nasr comments. A related initiative is to encourage manufacturers to submit comparability protocols (CPs) in NDAs to link the current CMC policy to this new quality assessment approach. CPs also can facilitate continuous improvement by reducing the need to file manufacturing supplements when a firm wants to change a manufacturing process or product attribute.

Speeding up generics

Similar initiatives are being adopted by CDER's Office of Generic Drugs (OGD), which continues to struggle with an increasing number of ANDAs and supplements. OGD expects to receive nearly 600 ANDAs and more than 3500 supplements this year, noted OGD director Gary Buehler at the advisory committee meeting. On average, OGD takes 18 months to approve an ANDA because all applications must sit in a never-diminishing queue, with no preference allowed for very complete or very simple submissions that could be processed quickly. ANDA approvals also are delayed by legal disputes and lawsuits, which appear to be intensifying (see sidebar, "Generic drug debate accelerates").

Buehler would like more authority to identify applications suitable for quick review treatment and to review groups of applications for the same product. But because Congress must authorize such a change in the "first-in, first-reviewed" generic drug approval process, Buehler is trying to streamline the ANDA review system internally.

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One initiative is to encourage manufacturers to calculate product specifications more carefully, which would reduce the time OGD staff must spend negotiating tighter limits. An OGD study found that 40% of all deficiencies in first cycle reviews relate to overly loose specifications, Buehler notes. He urges manufacturers to determine specifications on the basis of knowledge of the manufacturing process and critical product attributes and to provide a clear rationale for how specifications are selected.

This process, Buehler believes, will lead to more one-cycle reviews in initial applications and permit expedited handling of later supplements. Basing reviews on knowledge of the product and which manufacturing changes will make a difference represents "a fundamental change in thinking," Buehler says. The benefits for manufacturers are greater flexibility to improve manufacturing processes, more ease in making post-manufacturing changes, and fewer problems in plant inspections. Buehler is urging generics makers to demonstrate their expertise in drug product manufacturing by incorporating advances in pharmaceutical science and manufacturing technologies to improve product quality and reduce risk. Such an approach, he comments, will help generics makers challenge any perception that generic drugs are lower in quality than innovator products.

Greenwood to lead biotech industry

After a six-month search, the Biotechnology Industry Organization (BIO) selected Rep. James Greenwood (R-Pa) as its next president. He will replace retiring leader Carl Feldbaum, who headed the trade group since its establishment in 1993. Greenwood is completing his current term in Congress and will assume the new position in January.

Greenwood appears an ideal choice for the job. As chairman of the oversight and investigations subcommittee of the House Energy and Commerce Committee, the congressman has been involved in many of the research and reimbursement issues important to biotech companies. He played a lead role in recent revisions to the Prescription Drug User Fee Act and in negotiating the Medicare Modernization Act last year. A liberal Republican, he also has been an advocate for stem cell research. Greenwood said in July he would not have left Congress for any other trade association, but he sees the BIO job as an opportunity to advance the development of biological treatments critical for human health. At the helm of BIO, which represents more than 1000 large and small companies, Greenwood faces many challenges and controversies. The list includes "follow-on" biologics, intellectual property protections, and pricing and reimbursement, to name a few.

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Harmonizing standards

In addition to streamlining its own CMC review process and data requirements, FDA is looking to gain international agreement on risk-based quality standards through the ICH. In the past year, regulators in the European Union (EU), Japan, and the United States agreed to develop new guidance encouraging manufacturers to provide information that reflects a better understanding of critical product

and manufacturing design and process factors. The aim is to encourage risk-based approaches to manufacturing oversight and continuous improvement strategies in all global regions.

The first step involves crafting a guidance regarding the scope and content of quality summary information submitted in the drug product development (P2) section of the CTD's drug quality module. ICH participants approved a concept paper for this topic (Q8) in October 2003 and a draft standard at a June working group meeting in Washington, DC. The group hopes to gain approval of a final proposal at its next meeting, in November 2004.

The kind of manufacturing summary information called for in the Q8 proposal has been a common component of drug market applications in Europe, but new to the United States and Japan. This section presents information about formulation development, critical product attributes, and the design of the manufacturing process. The aim is to describe how product quality and performance is achieved and ensured by designing an effective and efficient manufacturing process. In EU applications, such a presentation often includes failed steps and problems encountered and resolved, but manufacturers generally have been reluctant to provide such information to FDA for fear of raising a lot of questions, explains Pfizer's Berridge, who leads the Q8 working group. Instead, manufacturers tend to give FDA huge amounts of data. Berridge and his colleagues hope the Q8 standard will discourage such practices and encourage the submission of information on the basis of a "true understanding" of a manufacturing process.

The envisioned Q8 guideline will contain a core document discussing how a manufacturer should describe its process for producing a fully characterized product through a well-defined process determined by an assessment of risk. Several annexes will provide examples of risk management approaches about specific dosage forms.

Generic drug debate accelerates

Provisions in the Medicare Modernization Act (MMA) were supposed to curb some of the infighting between innovator and generic drug companies, but the battle seems to be accelerating on all sides. One controversy involves "authorized generics" deals, arrangements by brand-name firms to license drugs facing patent expiration to selected manufacturers during the 180-day exclusivity period awarded to a generics rival. Generics makers Mylan Laboratories and Teva Pharmaceutical petitioned FDA to reject such deals, but the agency turned them down in July, stating that such arrangements do not violate FDA policy and can increase competition and provide earlier access to lower prices.

FDA sought to balance its position by denying a Pfizer petition challenging the generic firm practice of waiving (*i.e.*, selling) its right to a 180-day exclusivity period to another firm. Pfizer claimed allowing generics firms to relinquish exclusivity rights fosters patent challenges, but FDA claimed waivers were common and also encourage competition and lower prices. FDA further upset innovator firms by deciding to approve generic versions of synthroid (levothyroxine sodium) following years of bickering over bioequivalence testing of these medications.

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A related ICH initiative (Q9) aims to describe some of the tools and options for manufacturers seeking to control risk and for regulators wishing to adopt risk-based approaches to drug oversight and application review. The guidance will define how and when manufacturers and regulators may use preliminary hazard analysis, failure mode analysis, and other statistical tools in product development and regulatory scrutiny. The Q9 working group discussed a concept paper last November and moved forward in drafting a guideline in June.

Manufacturers also are working on what they hope will be a Q10 ICH guidance. This guidance would describe a quality management approach for achieving the processes and methods addressed in the other two standards. While Q8 focuses on designing quality into process and product development, and Q9 describes relevant risk-management tools and methods, Q10 aims to encourage industry to adopt a quality-systems approach to monitoring the manufacturing process. This topic was discussed at the ICH June meeting, but was put on hold by European and Japanese regulators who felt their plates were too full to take on another fairly complex initiative. The Q10 proposal fits with FDA's efforts to create a regulatory process that will support a continuous improvement model, but may take some time to begin moving formally through the ICH process.

Biogenerics battle heats up

While these and other disputes move into the courts, an even more contentious fight is building over FDA approval of "follow-on" versions of biotech therapies. The Hatch–Waxman Act provides a clear path for developing generic versions of conventional drugs, including insulin and human growth hormone, but does not permit FDA approval of generic biologics based on clinical data submitted by the innovator firm. FDA officials have been struggling to develop a draft guidance regarding testing and documenting the bioequivalence or comparability of biotech drugs but announced in June they would delay publication of guidance on "follow-on proteins" (now FDA's preferred term) until the agency explores more fully the scientific and legal issues involved.

At a hearing in June on key issues related to follow-on biotherapies before the Senate Judiciary Committee, chairman Orrin Hatch (R-UT) said that legislation was "inevitable," and urged biotech firms to stop stonewalling and engage in a constructive dialogue on legitimate scientific concerns. Some legislators want FDA to hold off issuing guidance until Congress acts, while generics firms believe that FDA guidance may spur the legislators.

FDA plans to address all relevant questions at a workshop this fall on product characterization of large molecules derived from biological sources. The aim is to develop a more complete and credible guidance document based on public discussion of all the technical issues. FDA staffers currently envision a draft guidance presenting general requirements for abbreviated applications for follow-on proteins, supported by specific guidances for certain products. **PT**

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