

# FDA Eyes Manufacturing Innovation

to Boost Drug Development

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New technologies, along with changes in agency oversight, may provide a critical path to make more new drugs available more quickly to patients.

**FDA** unveiled a report in March that maps out strategies for converting new biomedical discoveries into safe and effective therapies more quickly and efficiently. Although most of the specific proposals are not new to those familiar with drug manufacturing practices, the report shines a spotlight on the agency's desire to eliminate roadblocks to the development and approval of new drugs. This initiative to map "critical pathways" to drug development lends support to efforts by the Center for Drug Evaluation and Research (CDER) to streamline regulatory policies and better manage the review process.

## Removing R&D obstacles

A main objective for FDA is to reverse the recent decline in new drug applications (NDAs) filed with the agency, especially for new molecular entities. Former FDA Commissioner Mark McClellan frequently commented on the lag between gains in genomic and other cutting-edge biomedical research, and the development of new therapies able to improve public health. One of McClellan's last acts at FDA was to issue a report entitled "Innovation or Stagnation?—Challenge and Opportunity on the Critical Path to New Medical Products," which identifies obstacles and possible solutions for moving potential new medical products from laboratory concept to useful medicine ([www.fda.gov/bbs/topics/news/2004/NEW01035.html](http://www.fda.gov/bbs/topics/news/2004/NEW01035.html)).

The report notes growing interest in "translational research" that can help speed basic biomedical research into clinical testing. For the next step, FDA wants to provide new tools related more to downstream product development: preclinical

safety testing, clinical efficacy studies, and efforts to refine manufacturing processes.

It is noteworthy that FDA identifies product industrialization as the third dimension of this critical path in drug development. Although researchers and industry professionals often discuss the need to better assess drug safety and efficacy to accelerate the R&D process, this report also focuses on the difficulties in drug formulation, delivery, and manufacturing that block many potential medical products from reaching the market. FDA recognizes that outdated manufacturing systems and tools can stymie efforts to achieve high quality mass production of cutting-edge therapies—a problem that FDA believes is "highly underrated in the scientific community." In FDA's opinion, the failure to solve difficulties in product design, characterization, manufacturing scale-up, and quality control may "routinely derail or delay development programs and keep needed treatments from patients"—particularly therapies using new technologies, which frequently are more complex than traditional products and lack standard assessment tools.

At a recent Drug Information Association conference on chemistry, manufacturing, and controls (CMC) strategies, Liam Feeley, director of pharmaceutical R&D at Abbott Laboratories, estimated that up to 50% of the factors causing attrition of drug candidates during development could be related to CMC issues. He emphasized the importance of investing more resources in product formulation, characterization, and scale-up requirements to avoid wasted clinical studies and later manufacturing problems.

Janet Woodcock, currently serving as FDA acting deputy commissioner and author of the new critical pathways report, wants to work with the industry to gain more information about the root causes of product development failures. If a drug does not show efficacy in Phase III studies, she wonders how it got that far. Is the failure due to poor bioavailability, or too much variability in formulation? Gaining more insight into these issues is an FDA priority.

### New validation policy aims to overcome roadblocks

FDA issued a revised version of its process validation requirements in March, outlining a more flexible approach for assessing data to confirm the validity of the manufacturing process prior to distributing a newly approved drug ([www.fda.gov/cder/gmp/processvalidation.htm](http://www.fda.gov/cder/gmp/processvalidation.htm)). In this new compliance policy guide, the agency explains that under certain circumstances, manufacturers may not have to provide complete data from multiple commercial-scale conformance batches to bring a new product to market. FDA now refers to *multiple* batches instead of the traditional three validation or conformance batches at commercial scale previously considered necessary to document the robustness of a manufacturing process.

The revised guide still advises field staff conducting preapproval inspections to review all available validation data; inspectors retain authority to recommend withholding approval of an

application if important information is deficient or questionable or if the manufacturer has had previous validation problems.

However, companies with a good compliance history and that use a previously validated process may be able to begin product distribution before validation documentation is complete. In addition, manufacturers of orphan drugs or products with very short shelf lives, such as radiopharmaceuticals, may avoid wasted production activity by being able to distribute a product without completing conformance batches.

The new policy also allows more leeway in providing preapproval validation data for manufacturers that use new advanced engineering principles and control technologies able to provide continuous monitoring of a process to ensure batch quality. In such cases, FDA inspectors and reviewers

will consult with the company about what validation information is needed to distribute the product with sufficient assurance of quality and safety.

In the cases in which FDA permits a product to go to market before fully documenting process validation, postmarketing validation information gathering will be even more important. If significant deficiencies turn up later, FDA retains the authority to recall or seize the product. The new policy reflects FDA's thinking that "process capability can be determined in many ways," explains Woodcock, adding that validation activity does not end at the time of approval.

FDA considers this revised guide an important first step in its effort to update its process validation policy. As part of its GMP modernization initiative, the agency plans to revise its 1987 process validation guideline to further reflect "modern manufacturing principles, technology, and science."

### Making a list

FDA's next step is to create a critical-path opportunities list. Agency staffers are beginning to look for opportunities to develop standards or policies able to remove or over-

come specific obstacles to drug development. FDA leaders plan to seek additional suggestions from manufacturers, academics, and National Institutes of Health officials who are involved in its "roadmap" initiative

to improve clinical trials. One proposal, says Woodcock, is to develop a better FDA database of how manufacturing changes affect product performance, and to identify changes that are most critical to success.

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These initiatives were discussed at the April meeting of FDA's Science Board, along with proposals to devote a portion of the agency's \$135-million research budget to critical path projects.

In addition to calling for new efforts to improve drug development, the report acknowledges the need to build on initiatives to improve manufacturing processes and operations already underway.

**Updating GMPs.** FDA is continuing to implement this initiative to modernize current good manufacturing practices (GMP) standards, and plans to roll out additional policies in upcoming months. Under this program, the agency has established a pharmaceutical inspectorate and is training field inspectors to conduct more-targeted GMP inspections. A new high-level FDA panel has been formed to resolve dis-

putes involving manufacturing science issues, and FDA is encouraging international harmonization of GMP quality issues. FDA also has launched several collaborative efforts with manufacturers and researchers to articulate new approaches for understanding manufacturing science and risk management techniques.

**Promoting PAT.** A high-profile component of the GMP initiative is to encourage broader industry adoption of process analytical technologies (PAT) to reduce costs and increase the efficiency of drug manufacturing processes. FDA issued a draft guidance in September 2003 outlining a framework for agency review and

### FDA is developing new policies related to process validation and CMC review.

oversight of PAT manufacturing applications. Agency staffers are preparing a final guidance, and also are developing scientific principles and tools to support analytical and manufacturing control innovations. CDER's Office of Pharmaceutical Science (OPS) is establishing a PAT team to review applications and inspect facilities with PAT components; OPS has received six applications with PAT innovations and has begun to conduct PAT field inspections.

**New guidance.** In addition to several guidances issued as part of the GMP initiative (on PAT, 21 *CFR* Part 11, aseptic processing, and comparability protocols, among others), FDA is developing new policies related to process validation and CMC review. In March, CDER published a revised process validation policy to reduce requirements that delayed the launch of innovative new drugs in the past (see Sidebar, "New validation policy aims to overcome roadblocks"). CDER also is working with the industry to evaluate the best way to set product specifications that reflect product risk and consistency of manufacturing processes.

According to OPS Director Helen Winkle, these policy proposals reflect a move by CDER to devise a risk-based approach for submitting and reviewing CMC data.



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FDA has been discussing this issue for some time and now is stepping back to look at postapproval change requirements and comparability protocols to formulate a more workable approach. In the meantime, the agency may issue more targeted, informal guidances that address specific CMC issues raised in plant inspections.

**More collaboration.** A main objective of the critical pathway initiative is to launch

more joint efforts by FDA and manufacturers to address product development issues. FDA believes that its staff can help identify problems common to similar products because they have access to information about failed drug development programs that is not publicly available. "FDA holds the only broad, cross-cutting knowledge about how certain investigational products fail, why certain therapeutic areas

remain under-developed, and when certain development hurdles persist despite advances in technology that could mitigate them," the report explains. The agency seeks more public-private collaborative work on genomics, proteomics, bioinformatics systems, and new imaging technologies to help detect safety problems early, identify patients likely to respond to therapy, and address product design, characterization, and manufacturing issues.



### Changes at CDER

To better handle these new challenges, FDA officials are exploring ways to reorganize staff and procedures. Winkle is considering a major change in how OPS' Office of New Drug Chemistry (ONDC) reviews manufacturing data in applications. ONDC currently assigns review chemists to work directly with certain clinical review groups in CDER's Office of New Drugs (OND). With the emergence of new products that require special expertise to assess CMC data and manufacturing systems, Winkle plans to reorganize ONDC to establish more flexible review teams better able to adjust to changing work demands. ONDC's three chemistry review divisions now operate "in silos," Winkle comments, and may lack specific expertise to address issues related to a new product.

A team approach also will help integrate CMC reviews with field inspections, a main objective of the GMP initiative. This reorganization is likely to occur after much of CDER's staff moves to the new FDA office complex next year, a major change that will bring most drug clinical and chemistry reviewers under one roof for the first time in decades.

Similarly, OND Director John Jenkins is contemplating a reorganization of his six review offices. The current 10-year-old structure is based on clinical indications and product categories that no longer make sense in many cases, Jenkins notes. Some offices, such as the division of neuropharmacological drug products, are overloaded with applications, while others receive only a handful. The oncology office receives half of CDER's investigational new drug applications, but few NDAs. Jenkins expects to retain an indication-based structure, as opposed to Winkle's team approach, but plans to "improve the logical groupings of the office"

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to better balance the workload. One issue under discussion is whether to revise the current structure and process for reviewing over-the-counter (OTC) drugs. OTC manufacturers want to retain a separate OTC review office that can represent the value of these products when disputes arise, but this arrangement can lead to inconsistent review decisions.

The changes at OND will involve integrating reviewers of applications for biotech therapies into this indication-based review structure. Staffers transferred from the Center for Biologics Evaluation and Review (CBER) to CDER last year currently remain in a separate office for new drug evaluation. The plan is to add the oncology reviewers from CBER to the larger CDER oncology division and to disperse the others among CDER review groups. In OPS, though, Winkle expects to leave intact the Office of Biotechnology Products, which houses former CBER staffers who conduct research and review the manufacturing portions of biotech therapy applications. While the clinical

portion of biotech applications is fairly similar to that for drugs, the manufacturing sections are quite different.

Driving all these changes at CDER is pressure to maintain timely review processes despite increasingly tight resources. Although the volume of NDAs has not increased, OPS still has to process thousands of manufacturing supplements each year, plus a growing number of applications and supplements for generic drugs. To handle this growing work load, Winkle envisions a more risk-based review process that focuses more attention on the most critical CMC information, as opposed to equally evaluating all submitted data. She also aims to discourage late CMC data submissions and applications that fail to include needed information about pharmaceutical development.

One strategy for streamlining both drug development and approval involves increased manufacturer use of a "quality by design" method in drug development. This approach encourages manufacturers to invest more in CMC analysis up front to

gain a thorough understanding of a product's manufacturing process at an early stage in development. It may be useful to know, Winkle explains, that highly toxic reactions or disappointing efficacy results in clinical studies might relate to problems in product blending or other quality issues. Sometimes a blending process is so poor that the last pills in a batch have no active ingredient in them, and similar problems can arise from compressing and drying operations. The challenge to FDA and the industry is to better understand why a compressing process may not be working—perhaps the excipient is not appropriate, or the compressing machine has too little pressure. Earlier understanding of manufacturing and formulation can help a manufacturer demonstrate to FDA that the process is reproducible and well-controlled, which may reduce the regulatory burden and streamline product development. Manufacturing issues, Winkle notes, are more important than most people think. **PT**

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