From CGMPs to the Critical Path

FDA Focuses on Innovation, Quality, and Continuous Improvement—Inside and Out

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Janet Woodcock, MD, acting deputy commissioner for operations at FDA.

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As FDA continues to implement its risk-based approach to CGMP regulation and prepares for the work of the Critical Path initiative, agency staff focus on implementing quality systems in their own processes and on encouraging quality and innovation in the industry.

Two years ago, FDA unveiled an initiative entitled, "Pharmaceutical CGMPs for the Twenty-First Century: A Risk-Based Approach." The primary objectives of that initiative were to encourage innovation and new manufacturing technologies, to focus the agency's resources on the areas of manufacturing considered to pose the most risk, and to improve the consistency and predictability of the agency's work in ensuring drug quality and safety.

This year, the agency unveiled an important initiative that also focuses on the need for innovation, improvement, and predictability, but in drug development. The "Critical Path" initiative addresses the causes of the steady decline in approvals of novel drug therapies and raises the question of what the agency, industry, and other stakeholders can do.

These two initiatives are top priorities across the agency. Each office is examining how it can continue to expand the risk-based approach of the current good manufacturing practices (CGMP) initiative to encourage both increased innovation and quality in industry and the role it can play in facilitating the path to new drug development. At the same time, all parts of the agency are looking at ways to improve internal operations by applying the concepts of continuous improvement and quality systems. In doing this, the agency expects to streamline operations and to strengthen the scientific underpinnings of the agency's decision-making. This, it is hoped, will encourage innovation by increasing industry's trust that proposed improvements will be fully understood by the agency and regulated appropriately.

The critical path from discovery to market

The Critical Path initiative was launched in March with a report, "Innovation or Stagnation: Challenge and Opportunity on the Critical Path." The report describes the urgent need to modernize the "critical path" of drug development—the steps

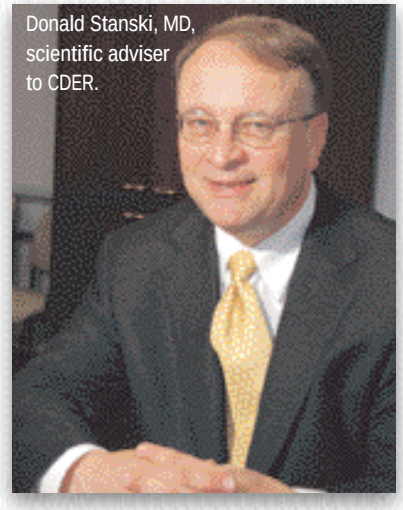
that determine whether a new drug discovery will become a safe and effective treatment for patients—to make the process more predictable and less costly.

The report notes that despite many advances in fields such as genomics, proteomics, and nanotechnology, and escalating private and public investment in drug research and development, the number of submissions of new drug applications (NDAs) for drugs with novel mechanisms of actions (new molecular entities, or NMEs) are declining. The key reason for this, according to the report, is that the advances in the basic sciences used in drug discovery have not been matched by a similar development in the applied sciences required to translate those discoveries into safe and effective medicines. As a result, too many drugs fail along the critical path between discovery and approved drug, in many cases after very significant investments of money and resources have been made. And for the successful drugs, the process is slow and costly.

The report calls on FDA to work together with academia, patient groups, industry, and other governmental agencies to identify and create predictive tools that will provide better answers about the safety and effectiveness of investigational drugs, faster and with more certainty. How this will take shape is still being determined. The first step is the development of an "Opportunities List" of the most pressing drug development problems and the areas with the greatest opportunities for rapid improvement and public health benefits. FDA is working to develop a list, and a docket for public input will remain open until 30 July 2004. The agency plans to publish a prioritized list this fall.

That list will be critical for determining what work will be done and who will do it. "FDA's primary role in this process will be that of convenor and collaborator," says Janet Woodcock, MD, director of the Center for Drug Evaluation and Research (CDER) and current deputy commissioner for operations of FDA. It is expected that industry will play a key role and that academia will be involved as well, both in conducting research as well as ensuring that education programs exist to support the kinds of research that are needed. The report also suggests that increased public funding of downstream drug development research by organizations such as the National Institutes of Health (NIH) also may be required. Woodcock stresses that a multidisciplinary approach is crucial. "The fact that the kind of work needed is so multidisciplinary is probably part of why it has been neglected," she says. "There isn't one discipline advocating for it."

The Critical Path report calls specifically for the creation of a "better product development toolkit," which consists of tools to address three main functions: assessing safety, demonstrating drug efficacy, and characterizing and manufacturing new drugs. The inclusion of manufacturing indicates that the agency continues to place importance on its ongoing work on CGMPs and process analytical technology (PAT). "A great opportunity exists for improving manufacturing processes," Woodcock says. She points out that part of the problem has been a lack of focus on manufacturing in both industry and academia. Because manufacturing is often viewed as a second-class sector, she says, studies in the physical sciences such as pharmaceutical engineering are not emphasized.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Donald Stanski, MD, scientific adviser to CDER.

"These concepts need to be driven to the very beginning of clinical development."

One Critical Path project already underway at FDA is developing ways to facilitate early, small-scale studies that could be conducted before a drug reaches the investigational new drug (IND) stage. Says Woodcock, "Before now, people had not thought too much about the need [to conduct] early proof-of-concept studies before getting into full drug development. There is a need to facilitate that, while maintaining the same safety for human subjects that we've always maintained."

Woodcock also recognizes that FDA regulation has played a role in slowing down innovation. "We are up front about that," she says. As a result, the agency is working on implementing a continuous improvement and quality systems model at the agency, in which processes are examined to identify areas for improvement. "We're very serious about these things," she says. "We will continue to push them forward."

Model-based drug development. One of the ways that the agency is looking to develop the "better product development toolkit" is by promoting the use of quantitative, model-based drug development in industry as well as knowledge about this approach within the agency. A leader in this effort is Donald Stanski, MD, who in January 2004 was appointed to the new position of scientific adviser to CDER, a one-year assignment. Stanski, a clinical pharmacologist and anesthesiologist, is teaching FDA staff about predictive models for drug development. The quantitative modeling approach involves charting the course of a disease, both untreated and treated with various drugs, and using data from clinical trials to develop statistical models that can then be used to create "virtual" clinical trials and to predict response rates. This approach also provides early feedback from clinical trials for use in modifying subsequent trials appropriately.

Based in the Office of Clinical Pharmacology and Biopharmaceutics, Stanski has been working closely with biostatisticians, biopharmaceutics reviewers, and medical reviewers to explain these scientific principles and how they can best be applied during regulatory reviews and ultimately in the industry. Stanski meets regularly with groups of 20–30 reviewers and has invited visiting professors to provide more examples of how the approach works. "The staff want real-life examples and demand evidence of the value," he says.

Although these concepts have been developed during the past 15–20 years and are currently used by some FDA reviewers, Stanski estimates that quantitative modeling is used in only 10–20% of cur-

FDA's move to White Oak

A new permanent commissioner is not the only change on the horizon at FDA. Between 2005 and 2010, most agency departments will move to a new campus located in White Oak (Montgomery County, MD). The venue will consolidate FDA's staff, who are now scattered among numerous sites in Rockville, Maryland.

Helen Winkle says the move will allow her to group her office's chemists, who are now colocated with the therapeutic divisions, into an independent CMC organization. "This will provide us with a lot of opportunities for more interaction within the disciplines as well as setting up a team-type of review that will help ensure that we have the right science behind the decisions we are making," she says. Winkle also expects that bringing the group closer to the laboratories will provide more opportunities for the review scientists to participate in research activities and to take advantage of current technologies.

CDER Director Steven Galson, MD, agrees that the new center will offer excellent opportunities. "We have been split up around Rockville for so long that people have forgotten, or they've never experienced, what it's like to be able to just walk down the hall to see your colleagues, rather than videoconferencing, leaving voicemail messages, or getting in the car and driving through traffic," he says. "Those things become such a habit and people forget how much efficiency we lose with those sorts of interactions. White Oak will be such a tremendous boost to how we communicate with each other and operate."

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Helen Winkle, director of the Office of Pharmaceutical Science.

Steven Galson, MD, acting director of CDER.

rent clinical development. "These concepts need to be driven to the very beginning of clinical development, not just to regulatory review," he says, adding that the agency is considering using drug and disease models as part of pre-IND meetings. Stanski believes the concepts can improve the efficiency of drug development. "You can reduce the number of clinical trials that are needed to gather critical information and also decide with better logic when to stop development," he says.

Fundamental shift

Steven Galson, MD, current acting director of CDER while Woodcock serves in the Commissioner's office, sees a fundamental shift of thinking in the Clinical Path initiative. "For the first time we're saying that the agency has a responsibility to contribute to innovation in drug development," he says. Once it becomes clear what CDER's role will be, that involvement will definitely require a shift of resources from other projects. "We'll have to prioritize carefully, because federal resources are scarce right now," he explains.

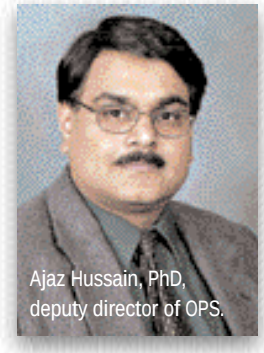
In the meantime, Galson's top priority is implementing the strategic plan set out for the agency by former Commissioner Mark McClellan before his departure. The first element of the plan is "efficient science-based risk management," an approach that CDER has been in the process of implementing for the past two years through the CGMP initiative. "We need to orient our regulations, including manufacturing regulations, around efficiency and risk, and make sure we're getting a good bang for our buck with our investment in manufacturing regulation," Galson says. He believes the agency's efforts will lead to fundamental changes in manufacturing and in how the agency regulates it. It's not going to happen immediately, he says, but it will be very positive. "There's no question that we are behind in efficiency in this area, and the agency is very focused on what we can do to improve that efficiency and innovation more generally. That is very, very important."

Galson is also leading CDER's effort to improve efficiency in-house by applying a quality systems approach to the Center's work. This involves identifying activities that are done differently in various divisions, and then implementing the best practices. He notes that the activities involved can range from administrative items, such as how minutes from review meetings with companies are handled, to scientific questions, such as whether certain components of a chemistry review are really needed. "In all cases," he says, "the agency is looking at whether there is a way to do things more efficiently and more consistently."

Down a common road

Quality systems and continuous improvement are also a key focus of the Office of Pharmaceutical Science (OPS), both internally and as part of its ongoing implementation of the risk-based CGMP initiative. Director Helen Winkle and Deputy Director Ajaz Hussain, PhD, also see a strong parallel between the Office's CGMP work and the thinking inherent in the Critical Path initiative. "It's a logical continuum," comments Hussain, noting that the third element of the Critical Path initiative is industrialization. "Both initiatives focus on the need for innovation and increased predictability and efficiency."

A key part of this focus on quality and efficiency is the PAT initiative, which started in early 2001 as part of the CGMP initiative. Hussain, chairman of the PAT steering committee, notes that the understanding of the goals of PAT has evolved. "Initially, people thought PAT was only about new technology such as near infrared (NIR) sensors," he says. "Now people understand that the main focus is process understanding." The key to PAT, Hussain emphasizes, is using the information gained to control and manage processes, adjusting them as needed to maintain the desired state, resulting in more consistency and quality.



Ajaz Hussain, PhD, deputy director of OPS.

OPS also is undertaking changes to improve its internal operations. This involves applying the quality systems approach as well as focusing on continuous improvement and effective knowledge manage-

CBER: life in the fast lane

The transition of regulation of many therapeutic biological products to CDER last year doesn't seem to have lightened the workload at CBER. The three groups of products that remain in the Center for Biologics—vaccines; blood and blood products; and cellular, tissue, and gene therapies—have the organization working in the fast lane and under the watchful eyes of the general public. CBER is constantly dealing with high-profile issues such as bioterrorism, new infectious diseases, and emerging technologies such as cell and gene therapies.

This work has brought about unique scientific challenges, notes CBER Director Jesse Goodman, MD. The center essentially has seen a transition to activities where very little is routine. "At any one time we're working with five or ten issues where there is no easy answer," he says. "Although this means that it's always interesting, it also means is that the quality of our decision making is important."

The immediate and vital importance of these areas does not allow the Center to play a passive role. "We try to identify needs before they become apparent, and then work with partners in industry, the Centers for Disease Control (CDC), and the National Institutes of Health (NIH) to identify the gaps, where possible solutions lie, and where those solutions are on their path to development," he says.

Recent activities include ensuring a sufficient nationwide supply of smallpox vaccine (a collaborative project with NIH and CDC) and the development of an assay to test blood for the West Nile virus. According to Goodman, CBER provides an important perspective in the handling of these issues because of its knowledge of various organizations' capabilities and the Center's ability to impart a practical, step-by-step approach.

Jesse Goodman, MD, director of the Center for Biologics Evaluation and Research (CBER).

James Cohen, acting director of the Office of Compliance and Biologics Quality at CBER.

In terms of biologics compliance, James Cohen, acting director of the Office of Compliance and Biologics Quality at CBER, says that generally, compliance has improved in recent years, but challenges remain. Noting that noncompliance is inefficient and costly, Cohen emphasizes the importance of building quality into the development and manufacturing stages of a biological product's lifecycle. This is especially true, he says, given the complexities associated with biological product manufacturing and because of the importance of ensuring sufficient supplies of many biological products. As part of the Critical Path initiative and furthering CBER's traditional risk-based approach to regulation, Cohen and CBER plan to provide expert guidance to manufacturers and encourage them to design and implement innovative quality programs at the earliest stages of clinical and product development.

A related goal is to increase the electronic reporting of biological product deviation reports (BPDRs). The agency recently revised the rule to streamline the process and make reporting easier. Cohen notes that the electronic reporting of BPDRs is an integral part of risk-based and quality systems management because it can improve the analysis of trends and accelerate follow-up, leading to improved compliance overall.

Another key part of CBER's quality management strategy, notes Cohen, is to extend the systems-based inspection program for biological products, already in use for blood and blood products, to cover source plasma and biological drugs as well. "This also will help broaden our risk-based approach," Cohen says. The systems-based program builds on the knowledge gained during previous inspections and focuses inspectional coverage on the operating systems within the manufacturing process that are considered to be the most critical to ensuring the safety, purity, potency, and effectiveness of the product.

ment. OPS plans to improve knowledge sharing through a peer-review system, in which reviewers will meet to discuss applications with other reviewers as well as staff from other disciplines.

Hussain believes that the quality systems and peer-review approach being implemented will increase industry trust in the agency, because it will improve the scientific foundation of the questions reviewers ask of sponsors. "We realize that if industry starts to submit more information and we respond with questions that show that we don't understand it, or in a way that increases the burden on companies, that will discourage them," he says.

Winkle adds that the agency's recent collaborations with industry organizations such as the Product Quality Research Institute (PQRI) and the American Society for Testing and Materials (ASTM) have been valuable. "It's been extremely useful to help us understand industry's problems and concerns," she says.

Quality systems and risk assessment in compliance

The risk-based CGMP initiative is an ongoing focus of the Office of Compliance. Office Director David Horowitz and Joe Famulare, director of the Division of Manufacturing and Product Quality, one of three divisions that report to Horowitz, believe that the division has made a lot of progress in this effort.

One recent application of the risk-based approach has been a new compliance policy guide, "Process Validation Requirements for Drug Products and Active Pharmaceutical Ingredients Subject to Pre-Market Approval." This guide avoids specifying that any precise number of commercial-scale validation or conformance batches must be manufactured. Instead, the new guide, which was created primarily for use by agency staff, focuses on the role of emerging advanced engineering principles and on control technologies for ensuring batch quality. "We're making sure that the full benefit of science is used as the basis for the robustness or validity of the process," notes Famulare. To further develop this approach, the agency plans to update the 1987 guidance on process validation within a year.

Another way in which the agency is expanding the implementation of the risk-based approach is in the development of a new guidance regarding the application of CGMPs to Phase I INDs. "This also supports the Critical Path because it facilitates the movement of new treatments through the early stages of development," Famulare notes. The agency has never required full application of the CGMPs for production for Phase I trials, but for many in

Office of Generic Drugs: stepping up the pace

As director of the Office of Generic Drugs (part of the Office of Pharmaceutical Science), Gary Buehler's top priority is handling the increasing workload of his office, which has escalated during the past two years. Until 2002, the office received around 350–360 applications per year. However, in 2003 this number jumped to 451, and projections for 2004 are between 550 and 600.

Buehler says the increase has been driven by various factors, including the large number of NMEs that were approved during the mid-1990s and that are now losing patent protection. The generics industry is growing quickly as well, especially overseas, and several new companies are submitting applications. Generic pharmaceuticals are also becoming more popular with consumers: generics currently make up more than 50% of prescriptions, up from approximately 45% only three or four years ago. Many consumers are mandated to use generics, either by federal government programs or by their private insurance companies.

Nonetheless, Buehler emphasizes that it is critical that the office handle the increased workload, and he is confident that they can. "We are a big part of addressing the high cost of prescription drugs," he says. "Everyone in my office recognizes this responsibility."

The Office's role in the Critical Path initiative involves facilitating the flow of information that generic firms need, including data for methods such as dissolution and bioequivalence studies. The office is developing on-line databases so that the agency can accommodate the approximately 900 requests for this information that are received every year. The dissolution method database is expected to be ready in about a year, but the bioequivalence database will take longer and will be an ongoing project.

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Gary Buehler, director of the Office of Generic Drugs.

industry it has not been clear which of the requirements apply. The guidance will provide greater articulation of those requirements, Horowitz says.

Like the rest of CDER, the Office of Compliance is also working to apply a quality systems approach to its operations; and at the same time, work is under way on a new guidance for industry on the topic. Famulare explains that the idea of the quality systems guidance is to augment 21 *CFR* Parts 210 and 211. "I think the new guidance can help industry to implement quality systems in their processes," Horowitz says.

Horowitz is encouraged to see the international focus on quality systems and risk assessment, and he points to two proposed guidances of the International Conference on Harmonization (ICH): Q8, titled "Pharmaceutical Development—Quality by Design," and Q9, titled, "Risk Management." In addition, Horowitz was looking forward to an industry proposal, expected to be presented at the June meeting of the ICH steering committee (not held at press time), for enhancing change management in manufacturing in a way that could lessen the need to file supplements for regulatory review. "This kind of action can really engage companies in being responsible for continuous improvement," says Famulare. "This helps foster innovation, which is an important principle of the risk-based CGMP initiative."

David Horowitz, director of the Office of Compliance.

Like their colleagues in OPS, Horowitz and Famulare stress that communication with industry is critical to the success of the risk-based approach. "Industry must develop and provide the data to demonstrate that certain low-risk areas are appropriate for reduced regulatory scrutiny and inspectional oversight," Horowitz says. "On our part," adds Famulare, "we are ensuring that our people have the right training to understand the risk principles and the science behind all these issues."

A new paradigm in CMC review

The OPS Office of New Drug Chemistry is working to encourage innovation and quality primarily through the institution of a new paradigm for the chemistry, manufacturing, and controls (CMC) review of new drugs. Director Moheb Nasr, PhD, prefers to call the new approach a "quality assessment paradigm," to emphasize the link between chemistry review and other critical pharmaceutical attributes related to product safety and efficacy.

One element of the new paradigm will be a better articulation of reviewer findings. Instead of just providing sponsors with a long list of deficiencies, the agency will provide a prioritized list that will indicate which deficiencies are the most critical because of their direct links to safety and efficacy. The agency also will list less urgent items that in some cases could be addressed after a drug is on the market, including changes to optimize a manufacturing process or increase product shelf life. This would allow critical drugs to reach the market faster and would reduce the need for multiple review cycles.

Nasr also believes that the number of CMC supplements required could be reduced by increasing the use of comparability protocols, in which companies lay out, at length, changes they plan to make, how those changes will be controlled, and sufficient assurance that the company understands the impact of those changes on quality and product performance. He suggests that once the protocol is approved, many of the changes could be reported only in the annual report, which would enable and empower industry to improve its processes.

To support the new paradigm, Nasr also plans to reorganize the office in a way that builds in flexibility to adapt to changes, rather than addressing them on an ad hoc basis as they do now. He also plans to increase the linkage between CMC review and the clinical issues of safety and efficacy. Currently, the agency's CMC reviewers are colocated in the 15 clinical divisions, but once the agency moves to its


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Joe Famulare, director of the Division of Manufacturing and Product Quality, one of three divisions in the Office of Compliance.


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Moheb Nasr, PhD, director, Office of New Drug Chemistry, in the Office of Pharmaceutical Science.


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Keith Webber, PhD, acting director of CDER's new Office of Biotechnology Products, in the Office of Pharmaceutical Science.

new offices in White Oak, Maryland (see sidebar, "FDA's move to White Oak), that will not be the case. Nasr sees that separation as a challenge and believes good communication will be needed to ensure that the relationship among chemistry, safety, and efficacy is maintained. "It is important that we don't look at chemistry and pharmaceutical quality issues in isolation," he says.

Nasr hopes the implementation of a new paradigm and restructuring will allow him to achieve another important goal: meeting more often with industry, so that the agency can be more of a partner in product development, potentially reducing review cycles and the number of CMC supplements. It is also important that companies challenge FDA, he says, particularly if they think the agency has made unreasonable requests. "Challenges from the outside help us create a vigorous organization with a stronger scientific base," he says.

The Office of Biotechnology Products in the Critical Path

The Office of Biotechnology Products (OBP), which was created when the regulation of most biopharmaceutical products was moved from the Center for Biologics Evaluation and Research (CBER) to CDER last year, may be in a unique position to participate in the Critical Path initiative. OBP has maintained the CBER structure of having staff who are both researchers and reviewers, and Acting Director Keith Webber, PhD, feels this could open up opportunities to address issues related to the Critical Path initiative. He notes that many biological products act on the immune system (either suppressing or enhancing it) and research into this area can help identify the mechanism of action and causes of adverse events (AEs). Such information is critical to establishing the validity of potency assays and finding ways to minimize AEs, he says. AEs are a frequent cause of the failures that occur in later stages of product development, a key concern raised in the Critical Path report.

In the meantime, Webber is ensuring that the final issues related to the CBER-to-CDER transfer of responsibilities are resolved smoothly. For example, OBP staff 's access to the CDER databases containing information regarding INDs and NDAs is expected to be completed soon. Ultimately, a new database will be created to provide uniform access to data for all products in CDER, including those transferred from CBER as well as those historically regulated by the Center for Drugs.

At the same time, Webber is preparing his office for PAT applications. He notes that the next round of PAT training will include reviewers from OBP. For biologicals, applying PAT to the early stages of production may be more challenging than for small-molecule drugs because biotech products have complex three-dimensional structures with multiple possible conformations and degradation pathways, making their characterization difficult. In later stages of the manufacturing process, however, the characterization process may be more straightforward for biotech products, he says, because at this stage they are usually liquid formulations or lyophilized products.

Conclusion

As the two-year anniversary of FDA's risk-based approach to CGMPs nears, offices across CBER and CDER continue to look for additional ways to apply the risk-based approach and encourage quality and innovation in industry. At the same time, the agency is applying a quality systems and continuous improvement model in-house, with the goal of strengthening the science base of its work. This, the agency hopes, will improve communication with industry, opening up opportunities for change. In addition, streamlining internal operations may free up resources for projects that will arise from this year's Critical Path initiative, which will involve a collaborative effort among FDA, industry, academia, and government agencies to pave the way to innovation and improved predictability and success rates in drug development.

OPS Director Helen Winkle seems to sum up the views of staff across the agency when she expresses her enthusiasm about the current opportunities before them. "We feel that the door has been opened up to us to make improvements that will help take the whole industry and the regulatory system to a new level," she says. "It's an exciting time." PT