ONDC's New Risk-Based Pharmaceutical Quality Assessment System

CDER's Office of New Drug Chemistry (ONDC) is responsible for reviewing the chemistry, manufacturing, and controls (CMC) section of new drug applications. Consistent with the CGMPs for the 21st Century Initiative, ONDC is establishing a modern, risk-based pharmaceutical quality assessment system to replace the current CMC review system. The new quality assessment system is intended to address the multiple challenges and difficulties facing the ONDC and to establish a framework to facilitate continuous CMC improvement and innovation in the pharmaceutical industry.

Challenges and Difficulties

ONDC is currently faced with multiple challenges and difficulties. They include:

- Inconsistencies in application quality combined with a lack of adequate pharmaceutical development information prevent us from taking full advantage of risk-based assessments. This leads to multiple CMC review cycles and a considerable increase in the number of postmarketing manufacturing supplements being submitted to the Agency.
- The need for an applicant to seek FDA prior approval through a supplement before effecting postmarketing CMC changes may be slowing the introduction of new technologies and innovations into pharmaceutical manufacturing.
- A lack of process understanding on the part of the applicant and submission of insufficient product knowledge information in applications could lead to tight product specifications at the time of approval, resulting in unnecessary recalls and drug shortages if a product batch fails to meet the specification.
- As a result of a heavy Agency workload and lack of resources, there is insufficient scientific dialogue between CMC reviewers and applicants during drug development prior to the submission of new drug applications (NDAs).
- Reliance on a single chemistry reviewer to evaluate the entire CMC section of a drug application throughout the entire life cycle does not facilitate optimum use of ONDC's limited resources or available expertise.
- Many valuable resources are being used to generate comprehensive CMC summaries and analyze raw data in CMC submissions — tasks that could be done more efficiently by applicants.

New Quality Assessment System

The ONDC is establishing a new, pharmaceutical quality assessment system to address the difficulties and challenges outlined above. The new system encompasses several initiatives, whose objectives are to allow rapid introduction of new technologies into pharmaceutical manufacturing and expedite review of applications without compromising the high quality of

drugs in the United States. The new system will focus on critical pharmaceutical quality attributes (chemistry, pharmaceutical formulation, manufacturing process, product performance) and their relevance to safety and efficacy. The system will rely more on the information provided by the applicant (e.g., the comprehensive quality overall summary (QOS) and the pharmaceutical development report) and less on the voluminous raw data currently being submitted (e.g., the executed batch records, raw stability data, methods validation package). The new system emphasizes quality by design in the evaluation of critical aspects of pharmaceutical quality; there is a strong focus on manufacturing science, integration of review and inspection functions, and use of modern statistical methodologies. We believe this approach will also greatly benefit manufacturers by providing them the flexibility to implement future manufacturing changes.

Restructuring ONDC

A key step in implementing the new quality assessment system is restructuring ONDC. Our goal will be to make ONDC a science-based organization that is more efficient, effective, and flexible in managing CMC issues and workload. Major features of the reorganization include the following:

- Dedicated premarketing and postmarketing divisions will be responsible for investigational new drug (IND)/NDA and supplement review functions, respectively, to increase the efficiency and effectiveness in both areas.
- A Pharmaceutical Assessment Lead (PAL) in the premarketing division, serving as a dedicated scientific liaison to a respective clinical division, will perform an initial assessment of each NDA before the NDA is assigned to a primary reviewer. The PAL will identify critical pharmaceutical quality attributes and develop a "Big-Picture" assessment protocol and timeline for completing the review.
- The PAL in the postmarketing division will perform an initial assessment of each CMC supplement to determine if it needs further evaluation. The PAL will perform a brief review for minor CMC changes or, if needed, develop an assessment protocol for major CMC changes before any assignment is made.
- A branch will be established to provide expert assessment and advice on manufacturing science, which will become an integral part of the new quality assessment system.
- Biopharmaceutics and microbiology evaluations will be better integrated into the quality assessment of new drugs.
- Facility inspection will be incorporated into quality assessment.
- A project management staff will be established to assist in the CMC quality assessment process.

The historical review process has relied on a single chemistry reviewer to evaluate the entire CMC section of a drug application throughout the product lifecycle — from IND through NDA, and eventual postapproval supplements. However, the nature and complexity of modern pharmaceutical manufacturing dictates a new system. In the restructured ONDC, the IND/NDA

and CMC supplement review functions will be separated to address critical CMC issues more expeditiously in both pre- and postapproval areas. When necessary, a small team comprising interdisciplinary scientists (i.e., chemists, pharmaceutical scientists, engineers, and/or others as needed) will be assigned to each submission. This new structure will optimize the use of ONDC's limited resources and available expertise.

Risk-Based Assessment and First-Cycle Approval of NDAs

Pharmaceutical manufacturing is evolving from an art form to a practice that is now based on science and engineering. Effective use of product knowledge information to evaluate manufacturing processes and establish specifications in regulatory decisions can substantially improve the efficiency of both manufacturing and regulatory review processes.

Currently, in many cases, insufficient pharmaceutical development information is being submitted to the FDA. Some of the development information used to support process validation during preapproval inspections is held at the manufacturing site for inspections and is never shared with the Agency. Few design considerations are described in submissions that clearly identify critical variables and their relationship to clinical performance. As a result, Agency reviewers often remain unsure about whether a change in a critical process parameter or end-product specification will adversely affect product performance. To address this uncertainty, a conservative regulatory approach has typically been adopted by regulators that often results in specifications and controls being based very narrowly on clinical trial lots. Such conservative approaches can lead to the approval of tests or restrictive acceptance criteria that may not be directly relevant to product performance, but that may increase the potential for product failures. Resulting recalls and drug shortages can be detrimental to the public and consume valuable industry and FDA resources.

The new assessment system will focus on critical pharmaceutical quality attributes and their relevance to safety and efficacy. Assessments will be risk-based, depending on the degree of understanding of the product and process demonstrated by the applicant, and they will be question-based and peer-reviewed.

Applying such a risk-based management approach to quality assessment will require that ONDC meet with industry more frequently on CMC-only issues during product development. The ONDC is committed to conducting such meetings with applicants to facilitate the use of new technologies and continuous improvement and to enhance the probability that all CMC issues are addressed during the first-cycle review of NDAs, thus, possibly reducing the need for postapproval supplements.

CMC specifications for a new drug product should be set as a result of a risk-based assessment, clinical relevance, process knowledge, and better use of modern statistical tools. We also recommend that pharmaceutical manufacturers always provide evidence that they have conducted appropriate risk analyses of the entire manufacturing process and that they have developed control strategies to mitigate risk of producing a poor-quality product. The FDA will

co-sponsor a scientific workshop in March 2005 to address issues related to setting CMC specifications.

The ONDC is currently considering different strategies to use comprehensive QOSs in pharmaceutical quality assessments. A comprehensive QOS can facilitate the development of a "Big Picture" assessment protocol by the PAL. If properly documented, a QOS can serve as a comprehensive summary of the NDA, thus eliminating the need to use ONDC's valuable resources to generate a summary as part of the NDA review. The QOS can facilitate the establishment of a database to track CMC reviews and identify critical CMC issues and review outcomes.

The ONDC endorses the principles underlying the upcoming International Conference on Harmonisation guidance *Q8 Guidance on Pharmaceutical Development* regarding quality-by-design, product knowledge, and process understanding. Our new ONDC assessment system is intended to encourage the adoption of these principles in pharmaceutical development and to facilitate the use of new technologies and continuous improvement by the industry throughout the life-cycle of the product.

Risk-Based Assessment of Postapproval CMC Changes

The new system will focus on risk-based assessments relying on available knowledge about the product and the manufacturing process. This system should facilitate continuous improvement and manufacturing process optimization. The newly formed postmarketing division expects to be able to streamline the supplement review process based on the degree of process understanding exhibited in the application and the extent of controls and quality systems that have been implemented throughout the applicant's manufacturing process.

This approach can reduce the frequency and extent of prior review of changes by FDA and expedite the manufacturer's distribution of drugs produced using an improved manufacturing process. In some cases, the new risk-based assessment system may eliminate the need for a manufacturer to seek the agency's approval of the change and instead permit the manufacturer to notify FDA of the change in an annual report. In other cases, the new system may allow earlier product distribution while FDA reviews a supplement describing the manufacturing change being used.

The ONDC has proposed the use of comparability protocols to implement numerous CMC changes. A comparability protocol provides evidence that an applicant has a firm scientific and technological understanding of the drug, manufacturing process, controls, proposed change, and potential effect of that change on the product quality. FDA's evaluation of a comparability protocol would include a determination of whether a change made in accordance with that protocol may be submitted under a reduced reporting category. Depending on the level of process and product understanding exhibited in the protocol, the change could be made with less prior review by FDA. A comparability protocol can also provide a mechanism to facilitate process improvement and/or process optimization. In some cases, a comparability protocol may offer a means to prevent or mitigate drug supply disruptions or shortages.

Role of CMC Reviewer in Preapproval and GMP Inspections

To ensure the integration of review and inspection functions at CDER, the new system will be coupled with a new examination of the roles and responsibilities of ONDC reviewers in product-specific preapproval and GMP inspections. As the pharmaceutical industry moves toward expanded implementation of process analytical technologies, quality-by-design, and combination products, the need increases for the CMC reviewer to play a larger role in the inspection process. The new system necessitates a science- as well as a risk-based approach during the inspection of facilities involved in active pharmaceutical ingredient and dosage form productions. Working in close coordination with the Center's Office of Compliance and Office of Regulatory Affairs, ONDC's review staff will be more directly involved as a partner in inspections. A more team-based format will evolve that allows firms to discuss and resolve science-based issues that arise during an inspection.

Conclusions

The ONDC will implement a new risk-based pharmaceutical quality assessment system that is dependent on a demonstration of product knowledge and process understanding by the applicant and focuses on critical quality attributes and their relevance to safety and efficacy. The ONDC encourages applicants to build pharmaceutical quality by design through product and process understanding and continuous improvement during drug development and throughout the product life-cycle. Regulatory decisions will reflect risk-based assessments relying on product knowledge reflected in the submission. The ONDC will be restructured to create the necessary organizational infrastructure that is capable of managing the new quality assessment system.