

CDER's Division of Post-Marketing Evaluation for Quality Assessment

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The new Division of Postmarketing Evaluation in the Office of New Drug Quality Assessment has implemented an improved system for managing the submission and review processes for postapproval chemistry, manufacturing, and controls change supplements.

In November 2005, the Office of New Drug Chemistry (ONDC) in the Center for Drug Evaluation and Research (CDER), US Food and Drug Administration, was restructured with the formation of the Office of New Drug Quality Assessment (ONDQA). This restructuring was undertaken to improve the regulatory oversight of new drug product development, manufacturing, and controls. An ONDC white paper was published discussing the objectives of the reorganization (1). These objectives include the fostering of innovation and the adoption of new technological advances in the pharmaceutical industry. In addition, the new office seeks to encourage the implementation of risk-based approaches that focus industry and the agency on areas critical to product performance and to ensure that products are developed, manufactured, and regulated using state-of-the-art scientific approaches. The new organization also will seek to enhance consistency of regulatory oversight of approved drugs and to better coordinate with other FDA quality regulatory programs, including integrated review and inspection.

The guiding principles as outlined in the ONDC white paper are:

- risk-based orientation;
- science-based policies and standards;
- integrated quality systems orientation;
- international cooperation;
- strong public health protection.

To improve the chemistry, manufacturing, and controls (CMC) review process for new drug applications (NDAs), investigational new drug applications (INDs), and supplements to NDAs for postapproval CMC changes, four divisions were established within ONDQA, three dedicated to address preapproval CMC issues and one dedicated to postapproval issues. The new organizational structure is shown in Figure 1.

The Premarketing Assessment Divisions handle NDA and IND reviews and the Postmarketing Evaluation Division handles all postapproval issues. The Postmarketing Division focuses exclu-

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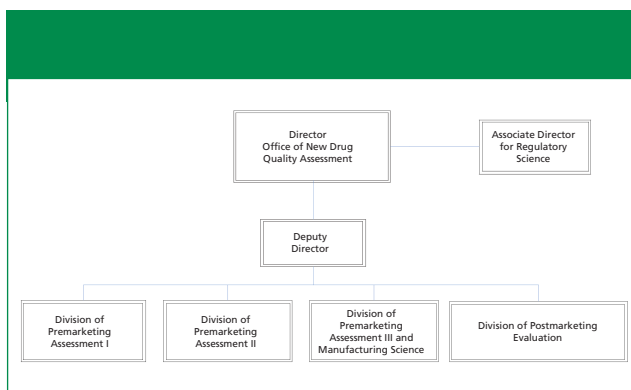


Figure 1. Four divisions were established within ONDQA, three dedicated to address preapproval CMC issues and one dedicated to postapproval issues.

sively on all postapproval issues, including supplements, annual reports, requests for advice on approved products, and drug shortages. Having a dedicated staff to address postmarketing issues also enables the Premarketing Divisions to focus entirely on preapproval issues, thereby leading to improved review efficiency and a higher rate of first-cycle NDA approvals. In other words, this organizational structure was intended to provide for a focused regulatory oversight on both sides of the product lifecycle, which should result in faster regulatory actions. Initial indications are that this is indeed the case.

Division of Postmarketing Evaluation

The Division of Postmarketing Evaluation has established a set of principles and objectives to guide the development of policies and procedures. These principles and objectives are:

- to foster the implementation of continuous improvement, innovation, and effective manufacturing changes within a process knowledge framework;
- to develop a streamlined review process within a risk-based framework, and capture knowledge from evaluation and review;
- to develop strategies to evaluate CMC supplements and to downgrade or eliminate certain CMC supplements based upon risk analysis.

The fundamental feature of these objectives is to apply scientific principles rigorously in making a risk-based assessment of the impact of postap-

proval changes as they may affect safety, efficacy, and quality of drug products. The new ONDQA structure, which separates preapproval from postapproval review, permits a more focused application of these principles in the assessment of CMC changes by staff

dedicated to postapproval changes. Having a comprehensive, global picture of postapproval CMC changes, including how data are generated and assessed, will permit the rational design of an appropriate quality-assessment system and use of risk-assessment tools suited to a scientific risk-based paradigm. The application of risk-assessment tools also will allow the allocation of resources toward issues where there may be an element of risk and away from those where there is minimal risk, to product quality and performance.

With the CDER move to new facilities at White Oak in Silver Spring, Maryland, the entire Office of New Drug Quality Assessment is located together. This is in stark contrast to the previous ONDC with its review staff assigned and colocated among the 15 clinical divisions. Having the office together should help ensure consistency in the way NDAs are reviewed. More specifically for the Division of

Postmarketing Evaluation, being together makes possible improved monitoring of workflow. The frequent requests from industry for comments and recommendations on proposals for qualification and implementation of CMC changes are centrally considered, thus ensuring that consistent advice is given. A database of requests for comment on scientific and regulatory strategies, along with the division responses, will help provide consistent recommendations. Also centrally managed within this division are drug shortage issues, with an emphasis on mitigating shortages, where possible, and expediting reintroduction of medically necessary drug products to the US market.

Organizational structure

The Division of Postmarketing Evaluation is organized into two branches consisting of 16 members each. The branches are led by the branch chief, who is responsible for three pharmaceutical assessment leads (PALs), 10 reviewers, and two project managers. Of the eight branches in ONDQA, the two postmarketing branches are denoted Branch VII and Branch VIII. Each is responsible for postapproval issues for drugs from designated clinical divisions. The current alignment is shown in the sidebar, “Products designated to the two branches of the Postmarketing Division.” Depending on designation, NDA applicants may contact the appropriate project manager with inquiries.

PALs serve as liaisons to the respective clinical division and assume the

Products designated to the two branches of the Postmarketing Division.

Branch VII

(Project manager: Teshara Bouie)

- Cardiovascular-renal products
- Neurology products
- Psychiatry products
- Anesthetic, analgesia, and rheumatology products
- Metabolism and endocrinology products
- Pulmonary and allergy products
- Dermatology and dental products

Branch VIII

(Project manager: Valerie Jimenez)

- Oncology products
- Imaging products
- Hematology products
- Nonprescription products
- Gastroenterology products
- Reproductive and urologic products
- Anti-infective products
- Antiviral products
- Special pathogen and immunologic products

responsibilities for handling the corresponding CMC issues that arise. They also are responsible for ensuring effective communication with the clinical division and with the clinical pharmacology and pharmaceutical toxicology (PharmaTox) disciplines. Although an assigned reviewer in the Division of Postmarketing Evaluation may not have been the one who historically had been the reviewer for a specific product, this does not present an immediate difficulty. There is a wealth of information available as well as an opportunity to directly consult with those who were the previous reviewers. Much attention is given to ensuring continuity of product knowledge to provide effective scientific review. The new Manufacturing Science branch, Branch VI of ONDQA, is an additional resource that provides manufacturing, engineering, materials science, and product development input and serves either as a team reviewer or a consultative reviewer.

Operations

The process for managing and performing the review of supplements begins with a triage of incoming applications, where a risk assessment is conducted to achieve three objectives. Based upon the risk assessment, the category of submission (*e.g.*, prior approval, changes-being-effected in 30 or 0 days) is either confirmed or adjusted. For prior-approval supplements, these are considered to be changes that are critical in nature and may have a significant impact on product quality and performance. For changes-being-effected supplements, the change is considered to be less critical and may have only a moderate potential to impact quality and performance adversely. In some cases the supplement is “downgraded” because the type of change is deemed to be less critical than reflected by the category under which the supplement was filed. Examples of the types of manufacturing changes which might be downgraded are changes to equipment and facilities, which are more appropriately considered GMP issues, or minor changes to an HPLC analytical method

(*e.g.*, to improve ruggedness or system suitability). As specific types and categories of changes are identified for “downgrading,” they will be communicated to the public.

The next step is to determine a review path so that an appropriate review consistent with the risk assessment can be performed, making the most of available resources.

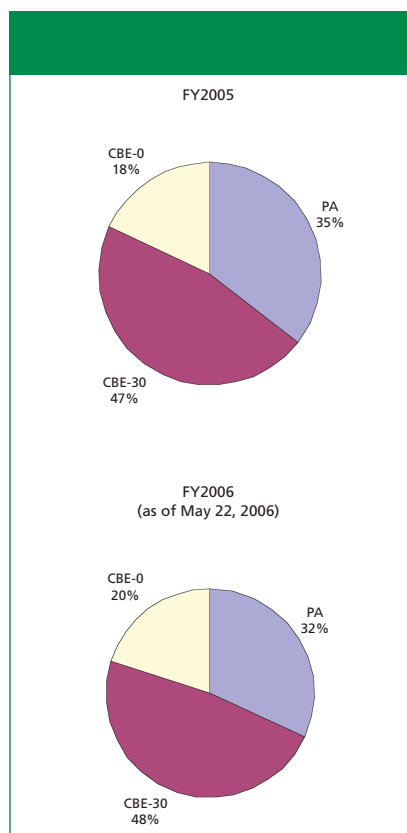


Figure 2. Nearly 2000 supplements to NDAs are submitted annually, of which approximately 35% are prior-approval supplements, as depicted in the charts in Figure 2.

The final objective is to perform an initial quality assessment (IQA) for supplements that will need further review by either a reviewer or a team. The IQA, performed by the PAL or a senior and experienced reviewer, is intended to capture the nature of the change proposed, the critical issues that may have an impact on product quality or performance, and an assessment of the risk of the change. Any consults or inspections that may be needed are identified, and suggestions are provided to the reviewer on how best to approach the review of the supplement. In addition,

the IQA will highlight the data package that was submitted to support the change, and, if the supplement category was changed, document the decision and rationale. When the review is completed, the review findings, including the adequacy of the data package provided, are documented.

Overarching these efforts, all of the information about postapproval CMC changes is captured in a database to analyze the supplement submission and review process with the intention of identifying best practices, simplifying the process, and finding ways to eliminate certain types of supplements and to reduce supplement requirements. In the past, there has been no comprehensive assessment of the supplement submission and review process. This analysis of the process will result in the identification of types of CMC changes and associated data packages that may not need to be submitted as they have been in the past. Reducing the number of prior-approval and changes-being-effected supplements is an achievable goal by communicating the science needed to support particular types of CMC changes to ensure that risk is mitigated. The findings will be shared and policies will be developed to facilitate the implementation of down-regulation of postapproval changes.

Performance

Nearly 2000 supplements to NDAs are submitted annually (*e.g.*, 1850 in 2005), of which approximately 35% are prior-approval supplements, as depicted in the charts in Figure 2.

Members of the new Division of Postmarketing Evaluation are developing criteria for potentially downgrading supplements and streamlining the review process. Although this effort has just begun, there has been some success worthy of reporting. Approximately 5% of the supplements received since November 2005 have been downgraded to annual reports. In terms of streamlining the process, approximately 30% of the submissions have been assessed with a brief review by a PAL or senior reviewer, followed by an immediate regulatory action. We expect these statistics to

improve as more experience is gained and additional categories of supplements are downgraded. The result will be more flexibility and faster approval for manufacturers to implement needed changes to products and processes.

Knowledge-rich submissions: quality by design

The key to a manufacturer's ability to implement manufacturing changes or to introduce new technologies is the demonstration of process understanding and process robustness. For the development of legacy products, where a wealth of manufacturing experience has been gained, it may be quite feasible to analyze the manufacturing processes and outcomes and thereby identify critical process parameters of unit operations and establish acceptable operating ranges. Additional experimentation, for example, through design of experiments, may help identify critical process parameters and acceptable operating ranges. In this fashion, these efforts may then allow for manufacturing adjustments and

changes within this defined boundary, referred to in ICH Q8, Pharmaceutical Development, as the "design space." When process knowledge and understanding have been demonstrated and the design space established, the applicant can reach an agreement with the division on the latitude and flexibility in

Risk is reduced with increased knowledge.

making continuous process improvements and introducing new technologies with minimal regulatory oversight. It should be recognized that, when evaluating the relative risk of a particular manufacturing change, the risk is generally reduced with an increased level of demonstrated knowledge.

Conclusion

The new Division of Postmarketing Evaluation in Office of New Drug Quality Assessment has been successful so far in implementing an improved system for managing the submission and review processes for postapproval chemistry, manufacturing, and controls change supplements. The system emphasizes the application of a rigorous scientific, risk-based assessment of the impact of chemistry, manufacturing, and controls changes. The highly dedicated and motivated staff have embraced this new approach and continues to apply these principles as the Division develops and matures within the new regulatory paradigm.

Reference

1. *ONDC's New Risk-Based Pharmaceutical Quality Assessment System*, http://www.fda.gov/cder/gmp/gmp2004/ondc_reorg.htm. ★



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