



New Drugs Regulatory Program Modernization: Vision, Strategic Objectives, and Impact

Kevin Bugin, MS, PhDc, RAC¹ · Janet Woodcock, MD¹ · Peter Stein, MD¹ · Khushboo Sharma, MBA, RAC¹ · Yonatan Tyberg, MHIA¹

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Abstract

In response to a rapid increase in drug development activity during the past two decades, the Food and Drug Administration's Center for Drug Evaluation and Research launched a multi-year effort in 2017 to modernize the program by which new drug products are regulated, known as the New Drugs Regulatory Program. Following a detailed analysis of FDA activities in new drug development, premarket review, and postmarket monitoring, the Office of New Drugs was restructured to therapeutically align its clinical offices and to add new cross-functional offices for regulatory support. An interdisciplinary review process for new drug and biologics applications was rolled out to reduce redundancy and produce review documents that effectively communicate the scientific basis for the regulatory decision. The investigational new drug (IND) review process was also streamlined. During the next 2 years, the modernization initiative will seek to attract and retain new scientific and regulatory staff, improve postmarket safety monitoring, increase efficiency of drug review via technology-enabled workflows, and standardize the capture and use of scientific data to inform future regulatory decisions. The modernization effort will position the New Drugs Regulatory Program to continually improve and adapt to innovations in science, technology, and drug development.

Keywords Reorganization · Program improvements · Modernizing FDA · Drug development

Introduction

The U.S. Food and Drug Administration's (FDA's) Center for Drug Evaluation and Research (CDER) has a mission to protect and promote the health of the American people by ensuring that drugs are safe and effective for their intended use, meet established quality standards, and are available to patients [1]. The New Drugs Regulatory Program (NDRP) consists of review staff from several different CDER offices, including the Office of New Drugs (OND), the Office of Translational Science (OTS), the Office of Pharmaceutical Quality (OPQ), and the Office of Surveillance and

Epidemiology (OSE). As part of this program, these review staff have the responsibility to provide regulatory oversight for investigational studies during drug development, make decisions regarding marketing approval and labeling of new drugs and biological therapeutics, and provide guidance to industry on a variety of clinical, scientific, and regulatory matters.

In 2017, CDER began a multi-year initiative to modernize the NDRP in an effort to advance leadership in the science and the regulation of new drugs. This effort came in response to mounting internal and external changes. Since the establishment of the new drug review processes and goals with the Prescription Drug User Fee Act in 1994 that kicked off the modern day NDRP, drug development activity has changed markedly in terms of both complexity and volume, increasing the regulatory workload. The innovative therapies under development have increased in complexity, due in part to the genomic revolution, advances in personalized medicine, and scientific progress that enabled an increased focus on rare diseases and disease subtypes. This created a need for new subject matter expertise on the

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✉ Kevin Bugin
kevin.bugin@fda.hhs.gov

¹ Center for Drug Evaluation and Research, US Food and Drug Administration, 10903 New Hampshire Avenue, Silver Spring, MD 20993, USA

part of regulators, and new analytical techniques and methods. The greater availability of data, including observational and other real-world data, prompted changes in the way the FDA manages and uses data for drug review and surveillance activities.

A vibrant drug development community has formed through increased public engagement in FDA activities by patient groups, the U.S. Congress, and other parties outside of the pharmaceutical industry. CDER has fostered this engagement with efforts such as the Patient-Focused Drug Development initiative [2]. The resulting outward focus necessitated improved transparency and communication of CDER's regulatory decisions and their underlying rationale.

This paper describes the strategies, activities, and anticipated or realized impact of CDER efforts to modernize the core activities by which it regulates new drug products. The results to date include a structurally reorganized OND and the implementation of improved processes for reviewing applications to develop and market new drugs. Longer-term initiatives are underway to strengthen postmarket safety monitoring, to enhance the process of soliciting expert advice from Advisory Committees, to attract and retain scientific and regulatory staff, and to implement strategies for more effective capture, management, and use of scientific and regulatory information (i.e., knowledge management).

Insights from the Diagnostic Phase

The NDRP modernization effort began in 2017 with a diagnostic phase during which CDER conducted a detailed assessment of the three core activities by which it regulates new drug products:

- Drug development (e.g., review of initial applications for Investigational New Drugs (INDs), subsequent amendments, and pre-approval sponsor interactions, including meetings)

- Premarket review (e.g., New Drug Applications (NDAs), Biologics License Applications (BLAs), and efficacy supplements)
- Postmarket oversight (e.g., safety of and changes to approved drugs)

The modernization team worked with senior members of the NDRP at various levels of the organization to map existing drug review and surveillance processes to help characterize problems, recognize practices that were working, and identify which processes could be streamlined. A survey of staff was conducted to assess change readiness at the individual and organizational levels, and to develop a perspective on the perceived value of improvements (Table 1).

The diagnostic phase yielded several insights. First, it was clear that the processes used to review drug applications and monitor the safety of marketed drugs could benefit from standardization and increased efficiency. For example, some teams had developed simple but elegant solutions to triage and prioritize new protocols and protocol amendments, but CDER lacked a way to disseminate and institutionalize these successful practices. Second, an opportunity existed to improve the core outputs of the NDRP, namely the written reviews of NDAs, BLAs, and INDs. Specifically, CDER sought to clarify and increase the transparency of its regulatory decisions by making available more concise statements of key findings, as well as supporting evidence, analysis, and rationale, including areas of disagreement among reviewers. This could be achieved through reorganized drug review documents that focused on key issues and integrated rather than compiled reviews from discipline-specific teams.

The third insight unveiled by the diagnostic was a need to strengthen the tools and technology that drive the NDRP. These included drug review workflows, platforms used to analyze safety and efficacy data, and reviewers' ability to access and use scientific and regulatory precedents to inform and increase the consistency of future decisions. Finally, staff recruitment and retention data, along with historical

Table 1 Selected Findings From Staff Survey to Inform Modernization of the New Drugs Regulatory Program.

Survey Objective	Selected Findings
Evaluate readiness for change	Recognition of the opportunity that change presents Personal commitment to support change Readiness for concrete, tangible change Variability in conviction of the need to change
Assess satisfaction	Staff feel they are part of a high-performing organization Experience of strong leadership and mentorship Experience of attractive work culture and work environment
Solicit ideas for improvement	Greater process standardization for consistency Improved technology, tools, and processes to increase efficiency Automation to reduce repetitive, manual work Support for data analysis to free scientists for data interpretation

workload, demonstrated an urgent need to fully staff the offices and divisions in OND, to reorganize to better align FDA scientists with the therapeutic areas under regulation, and to add new specialized talent, such as medical editors and clinical data scientists. Retaining and motivating staff required clearer career paths, more opportunities for advancement, and innovative professional development opportunities.

Strategic Objectives and Workstreams

Following the insights gained in the diagnostic phase, senior leaders of the NDRP laid out an aspiration for the modernization in terms of six strategic objectives (Table 2). These objectives helped create a clear vision that could be consistently communicated to staff and external stakeholders. For each objective, a guiding principle or goal was articulated, followed by the key actions needed to achieve the objective and to measure progress and impact. To implement this plan, seven workstreams were established:

- NDRP Reorganization
- Integrated Assessment of Marketing Applications
- IND Review Management
- Postmarket Safety
- Assessing Talent & Talent Development and Management

- Knowledge Management
- Advisory Committees

Activities under the first three of these workstreams were largely completed in 2020 and are discussed below. The remaining four workstreams have begun to implement modernization activities that will continue into 2021.

New Drugs Regulatory Program Reorganization

The objectives of the NDRP reorganization were to enable regulatory scientists to increase their focus on science, to promote greater efficiency and consistency in the review process, and to increase professional development opportunities. A phased, 6-month organizational restructuring of OND and related changes in OTS and OPQ was completed in March 2020 with minimal disruption of ongoing regulatory work. OND clinical offices were realigned according to interrelated disease areas to enhance scientific exchange and collaboration (Fig. 1). For example, the new Office Immunology and Inflammation comprises divisions with expertise in rheumatology, pulmonology, allergy, and gastroenterology. Within these clinical offices, divisions were also reorganized to be more consistently disease-area focused. In addition to promoting collaboration on common therapeutic issues, the new office structure enables cross-functionality of staff in the event of workload changes. The number of OND

Table 2 Strategic Objectives of the New Drug Regulatory Program Modernization.

Objectives	Guiding principles for modernizing the NDRP
Scientific Leadership	<p>We will grow our scientific expertise and clarify pathways to regulatory approval.</p> <ul style="list-style-type: none"> • Expanding the armamentarium to address unmet medical needs is an important part of our public health mission. • Towards that end, we will proactively collaborate with academic medical scientists and patient/disease advocates, evaluate scientific gaps, and strategically foster drug development.
Integrated Assessment	<p>We will critically, collaboratively and consistently assess whether information in submissions meets statutory and regulatory requirements.</p> <ul style="list-style-type: none"> • We will take a new approach to document our assessments, developing a more integrated, cross-disciplinary document to foster collaboration and reduce redundant information. • Our assessments will be rigorous, risk-based, and clinically relevant; focus on the key issues; and incorporate the patient perspective.
Benefit-Risk Monitoring	<p>We will establish a unified post-market safety surveillance framework.</p> <ul style="list-style-type: none"> • To effectively protect the American public, we will systematically monitor the benefits and risks of approved drugs across their lifecycles.
Managing Talent	<p>We will attract, develop, and retain outstanding people.</p> <ul style="list-style-type: none"> • We will use 21st Century Cures Act authorities to recruit and retain technical, scientific and professional experts, and eliminate our backlog of vacant positions.
Operational Excellence	<p>We will have a dedicated focus on operational excellence.</p> <ul style="list-style-type: none"> • We will enhance our ability to address OND's large volume workload through greater process standardization and better defined roles and responsibilities. • This will improve operational efficiency and enable our scientists to focus on science, not ancillary tasks.
Knowledge Management	<p>We will facilitate knowledge management.</p> <ul style="list-style-type: none"> • Vast and diverse information is submitted to and generated by the New Drugs Regulatory Program. • We will make it easy for our staff to find and use scientific and regulatory precedents. • This will reduce manual work time, increase the speed and efficiency of submission assessment, and increase the consistency and predictability of regulatory decision-making.



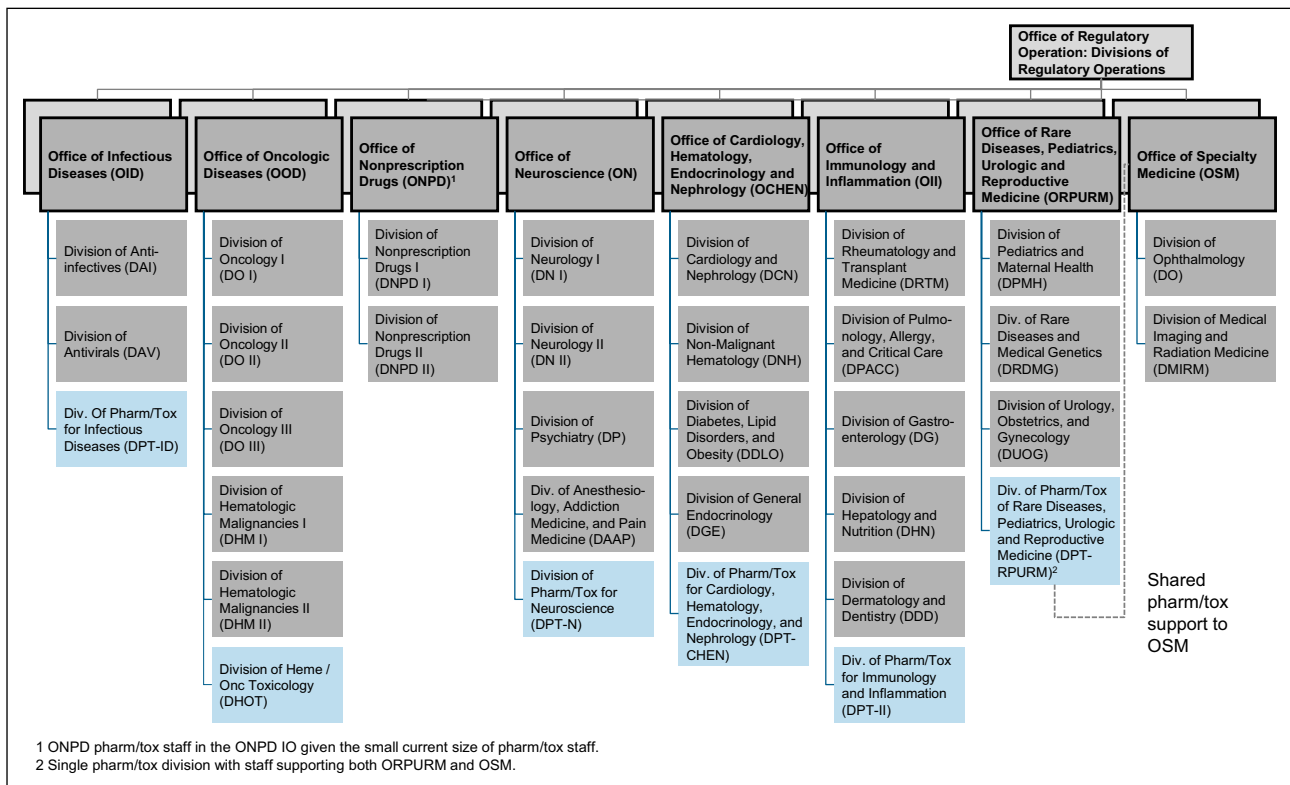


Figure 1 OND’s Reorganized Clinical, Regulatory, and Pharm/Tox Structure. 1. ONPD Pharm/Tox (PT) staff in the ONPD IO given the small current size of P/T staff. 2. Single P/T division with staff

supporting both ORPURM and OSM; PT DD will have dotted line reporting to ORPURM and OSM for P/T issues, and solid line to ORPURM Office Director for PMAP, etc.

offices that oversee review divisions was increased from six to eight, and the number of clinical divisions from 19 to 27.

New divisions of pharmacology/toxicology were also created to support each of the new clinical offices.

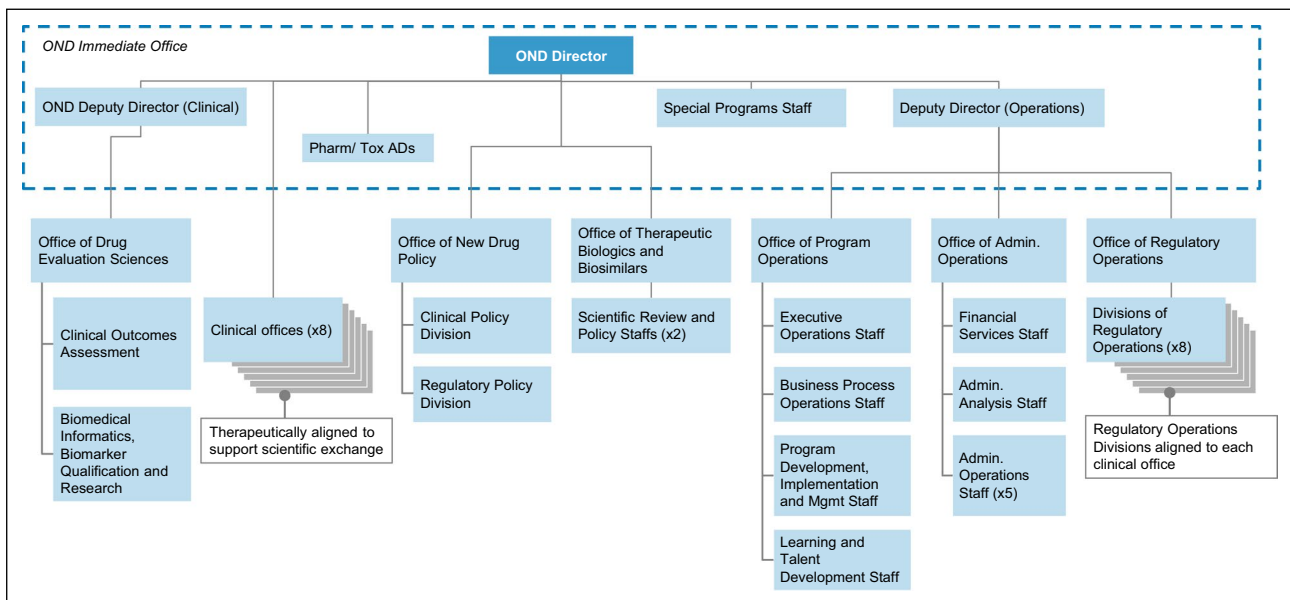


Figure 2 OND’s New Overall Structure.

In addition to realignment of the clinical offices, an infrastructure of six new cross-functional offices was created to provide program, administrative, and regulatory operations support (Fig. 2). For example, the Office of Drug Evaluation Sciences provides expertise in clinical outcomes assessment, biomedical informatics, and biomarker qualification across the NDRP for enhanced efficiency and consistency. Similarly, the Office of New Drug Policy provides consistent, cross-office input on how to apply regulation and statutes to the challenging clinical and regulatory policy issues faced by reviewers. The Office of Regulatory Operations now drives operational consistency and efficiency through ownership of the regulatory process and dissemination of best practices across the organization.

The restructuring of OND required corresponding changes in the Office of Translational Sciences (OTS) and the Office of Pharmaceutical Quality (OPQ), which also support OND's clinical structure. OTS provides OND with biostatistics and clinical pharmacology expertise, while OPQ supports pharmaceutical quality via establishment of quality standards and inspections of manufacturing facilities.

Integrated Assessment of Marketing Applications

The largest undertaking of the modernization effort has been the gradual implementation of a newly envisioned process for the assessment of marketing applications (i.e., NDAs and BLAs). In the traditional review process, siloed work generated a compendium of discipline-specific reviews that were frequently overlapping and redundant. In the new process, scientific review staff from relevant FDA organizations form an interdisciplinary team to identify and discuss a set of key issues related to safety and efficacy of the product proposed for marketing. The team then co-authors a review structured around these key issues and the underlying benefit–risk framework. This process, known as Integrated Assessment of Marketing Applications, and the resulting integrated review has begun to replace traditional reviews. This new Integrated Review yields review documents that clearly describe the FDA's analysis of the scientific issues raised by the application and effectively communicates the basis for the regulatory decision [3]. The newly created support roles of medical editor and clinical data scientist enable the review process and its documentation, allowing reviewers more time to focus on scientific assessment. A virtual public workshop [4] is planned for October 2020 to seek public comments and feedback on the Integrated Assessment process and Integrated Review document. (See companion paper on the Integrated Assessment process.)

IND Review Management Workstream

Changes to scientific review processes for INDs were proposed to address inconsistent and redundant documentation of reviews, and lengthy review timelines in which sponsors did not always receive the FDA's non-hold comments in time to modify their study designs prior to launch. Standardized review processes and issue-based templates were implemented to promote consistency, quality, and timeliness of review documentation. The first initiatives focused on the 30-day review of the initial IND application and on the review of select clinical protocols and amendments considered priority. A cross-functional review template for the 30-day safety review compiles critical data and assessments by multiple disciplines all in one place and conveys the overall decision for the initial IND. Complementary discipline-specific templates rely on a question-based format to focus the review on key issues, with free text for additional information. The new standardized IND review templates document internal discussions and external comments to the sponsor and contain standardized input fields to facilitate the leveraging of data from past reviews for future activities. These templates have been further enhanced by incorporating into a modern workflow management system.

Implementation and Impact of NDRP Modernization

After a period of time spent on design, each workstream developed an implementation and dissemination plan. Implementation began in late 2018. For most new activities, the modernization team opted for a phased, iterative implementation whereby changes were adopted by a few divisions to generate feedback and refinements prior to a broader rollout. To support implementation, a governing body met monthly to provide oversight, review progress, and address bottlenecks. "Change ambassadors" of various disciplines were selected to promote early adoption, answer questions, and gather feedback. Timelines and checkpoints were designed to be ambitious, yet flexible and were revised to respond to changing conditions (e.g., the FDA's response to the coronavirus pandemic).

For each of the six strategic objectives, the realized or anticipated impacts of modernization are described below:

Scientific leadership The first strategic objective aims to elevate scientific expertise and create clearer pathways to drug approval in areas of unmet need, ultimately expanding the armamentarium of approved drugs in these areas. Anticipated outcomes include innovation in trial design, sustained progress for clinical pipelines, innovation in regulatory policy and pathways, and increased recognition of FDA's leadership in drug development through increased citations

and references to CDER's work. The reorganization of the NDRP, which included the establishment of the new Office of Drug Evaluation Sciences and the Office of New Drug Policy, has begun to support these outcomes. For example, since the establishment of the OND Policy managed bulleted guidance program, the FDA has published more than 100 bulleted, disease-specific guidance documents.

Integrated Assessment This strategic objective aims to create an effective, issue-focused, and interdisciplinary drug application review process, and review documents that effectively and transparently convey regulatory decisions. The new Integrated Assessment of Marketing Applications process is well into implementation; as of August 2020, nine Integrated Review documents have been completed and 16 are in progress. In addition, at the time of submission of this manuscript, 470 reviews of INDs have been completed using the new IND review process.

Operational Excellence Technology-enabled regulatory workflows are critical to improving efficiency and helping CDER scientists to focus on the science of their work. The implementation of standardized processes for drug application review with quality controls is expected to reduce time spent on ancillary tasks and increase time spent engaging with sponsors and developing insights on new topics in regulatory science. The workflow for the 30-day safety review of initial INDs and Newly Identified Safety Signals was implemented in early 2020, and it is expected that several new technology-enabled workflows will be implemented by the end of this calendar year, and as many as 20 in total over the next 3 years.

Benefit–Risk Monitoring Improved interdisciplinary monitoring of the risks of new and marketed drugs supports treatment decision-making and protects public health. The anticipated impacts of this objective are earlier identification of potential safety signals and effective cross-disciplinary management of safety-related issues. A Drug Risk Management Board was recently established as a cross-CDER body responsible for coordinating decisions and responses to major safety issues of marketed products. In April 2020, the FDA published policies and procedures that streamlined the process for identification and review of Newly Identified Safety Signals, with clearer criteria for which signals should be tracked and a requirement to notify sponsors within 30 days of opening a new evaluation [5].

Managing Talent To attract, develop, and retain outstanding people, CDER aims to recruit talent from new sources and to reduce attrition through improved incentives, professional development opportunities, and a stimulating scientific work environment. For example, in 2019 the Office of New Drugs (OND) saw 158 new hires and 46 net new hires, the highest numbers in 3 years. To improve development, a competency framework has been established to set expectations for staff and enable more objective assessments; new

competencies have been drafted for about 80% of OND staff, with completed rollout expected in 2021.

Knowledge Management Many types of data are submitted to and internally generated by the FDA. CDER is establishing ways to capture and use various information and data to leverage the knowledge gained from its regulatory experiences and to use precedents to inform future decisions. Expected outcomes include standardized data capture during application review processes, improved access to searchable regulatory information, and the ability to share data internally and externally. As a first step, use cases were gathered to study how knowledge management-enhanced workflows could support daily work. Of approximately 200 use cases, 61 were categorized as highly impactful activities, indicating where knowledge management efforts could be focused. Technology-enabled workflows are anticipated to enable future use of more advanced solutions involving artificial intelligence and machine learning, for example natural language process to extract knowledge from regulatory archives.

Discussion

A rapidly changing drug landscape is requiring the FDA to grow its expertise, strengthen its review of drug programs, and keep pace with science. In its first 3 years, the NDRP modernization effort has implemented a structural reorganization, created more integrated and streamlined processes for review of INDs and NDAs/BLAs, and begun efforts to grow scientific leadership, address staffing shortfalls, and manage regulatory data. As some workstreams are in the early stages of iterative implementation, it will take time to realize these activities and their impact for CDER and for patients.

Modernization is not a one-time event, but a means to position the NDRP to continually improve and remain responsive to innovations in science, technology, and drug development. CDER now has a program in place for diagnosing issues, assessing potential opportunities for improvement, and designing improvements in collaboration with colleagues in and outside of the NDRP. This program, in partnership with business process operations staff in OND, will support continuous improvement of modernization initiatives once they are implemented, while CDER continues to explore new ways to make improvement.

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Compliance with Ethical Standards

Conflict of interest

The authors declare that they have no competing interest.

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