COMMENTARY

Case Study for Lean Management in the Public Sector: Improving Combination Product Review at the Food & Drug Administration

MJ Rappel*, NL Hunter, AI Alexandrow, KO Hair, RE Sherman and RM Califf

INTRODUCTION

Therapeutics known as combination products because they combine drug, device, and/or biologic elements can offer important advantages relative to single-modality products. However, regulatory policy in this arena has lagged relative to increases in product submissions and complexity of these products. In this article we describe how the US Food and Drug Administration (FDA) applied Lean Management methods to improve and streamline the process by which different FDA centers and offices coordinate review of combination products.

Therapeutic products that combine drug, device, and/or biologic elements account for an increasing share of medical products. The global market for these combination products is expected to grow at a compound annual rate of 5.6% from 2012–2017,1 higher than rates projected for medical devices2 or prescription drugs.3 Combination products such as drug-eluting stents, prefilled infusion pumps and inhalers, transdermal patches, antibody-drug conjugates, and even some digital health technologies comprise approximately one-third of all medical products under development.4 Combination product submissions to the FDA including new technologies increased 17% in 2015 vs. the previous 5-year average.

Combination products offer potential advantages relative to single-modality products, including fewer adverse effects, improved adherence, controlled drug release, and targeted delivery. However, regulatory policies have not kept pace with the growing number and complexity of these products.5

IMPROVING COMBINATION PRODUCT REVIEW

In 2002, the FDA Office of Combination Products (OCP) was established to enhance the transparency, predictability, and consistency of combination product regulation and ensure timely clearance/approval. Although OCP decides where a product is reviewed, review activities themselves take place within the FDA’s medical product centers. A combination product is generally assigned to a lead center, which may seek consultation from other centers overseeing the product’s other constituent parts. Thus, a drug/device combination typically undergoes review at the Center for Drug Evaluation and Research (CDER) and the Center for Devices and Radiological Health (CDRH). Because expeditious review requires seamless cross-center communication and collaboration, the FDA must build partnerships that foster efficient, effective review, ultimately enabling more and better treatment options for the public.

In 2015, external studies6,7 and reports from the Government Accountability Office underscored the importance of cross-center collaboration and the need for a comprehensive strategy for managing combination product review. External studies highlighted inefficiencies that could delay approval and, ultimately, patient access to therapeutics. A parallel FDA study8 highlighted internal issues that aligned with external findings (Figure 1). Comprehensive assessment of these reports revealed several opportunities for improvement: (i) clearly defining major processes associated with combination product review; (ii) improving cross-center coordination throughout application review to ensure predictable, standardized touchpoints within the FDA and externally; (iii) officially establishing, defining, and communicating roles and responsibilities for OCP, the reviewing center, and the consulting center(s); and (iv) documenting a streamlined process for quickly and transparently designating combination products.

Further analysis identified cross-cutting initiatives that would enable review improvements: (i) enhancing cross-center collaboration through improvements to the Intercenter Consult Request (ICCR) process; (ii) defining a structured process for sponsors to send jurisdictional inquiries to the FDA early in product development; and (iii) establishing a Combination Products Council (CPC) with authority to develop and implement new cross-cutting policies that promote development of innovative combination products.

LEAN MANAGEMENT

Feasibility studies determined that among the initiatives described above, redesigning the ICCR process would capitalize on several identified opportunities and have significant, long-lasting impact for all combination product submissions, including products with mature regulatory pathways (e.g., drug-eluting stents) as well as novel products (e.g., antibody-drug conjugates; digital health technologies). The Commissioner selected Lean Management to address the redesign
The Lean Management Staff within CDER’s Office of Strategic Programs facilitated strategic cross-cutting process improvement projects, focusing on the human drugs program. One example includes a partnership with >25 stakeholders from CDER’s Offices of Communications, New Drugs, and Surveillance & Epidemiology to document the existing Drug Safety Communications process, identify opportunities for improvement, implement solutions, and track associated metrics—efforts culminating in a 75% reduction in total time required for process completion.

Although the FDA has used Lean since 2012, implementing the standard Plan-Do-Check-Act approach for the ICCR redesign would represent its first application to an agency-wide problem. Leveraging previous successes with CDER-focused projects, Lean Management Staff helped apply and transfer knowledge of Lean tools and principles to this broader process to improve communication and coordination among groups overseeing development, review, and clearance/approval of combination products.

**STEP 1: PLAN**

The project was launched by gathering information through internal stakeholder interviews (including centers and the OCP) to validate report findings and benchmarking of ICCR processes against other cross-center regulatory activities. Lean Management Staff then facilitated three cross-center stakeholder sessions structured around (i) performing a capabilities assessment; (ii) documenting current ICCR processes and identifying opportunities for improvement; and (iii) proposing improvements and defining the future-state ICCR process.

**Capabilities assessment**

We selected the Lean’s Strengths/Weaknesses/Opportunities/Threats tool to assess the capabilities of the FDA organizations involved in the ICCR process. Each organization performed a self-assessment and an assessment of the other organizations; these were used to identify hierarchical themes for each capability category and (later) to identify opportunities for improvement and craft specific solutions.

**Current-state ICCR process documentation**

Lean process mapping visualizes “what, how, and who” for each process. It creates clear visual documentation, enabling shared understanding of a process and meaningful dialog; it also permits prompt identification of bottlenecks and opportunities for improvement.

The OCP and centers independently developed current-state maps for the original ICCR process, starting when a consult was received or sent and ending when the consult was completed. Documenting the process from multiple perspectives enabled robust team-based discussion that highlighted both waste and opportunity within the existing process. Outcomes resulting from the mapping sessions were assigned priorities based on potential impact and expected feasibility of implementation.

**Future-state ICCR process**

Root-cause analysis of problems highlighted during current-state process mapping identified underlying issues to be addressed. Solutions were developed, with a preference for improvements that could be implemented with readily
available resources. Process enhancements and their application to external pain-points and internal challenges are summarized in Figure 1. Figure 2 illustrates the impact of process enhancements by contrasting multiple hypothetical submission pathways under existing processes with the new single standardized pathway. Although the frequency and extent to which these hypothetical pathways are followed is unclear, standardization around the new process, including metrics detailed below, will enable future improvement efforts.

The new future-state ICCR process was vetted thoroughly with OCP and the centers to ensure alignment with proposed changes. It was then reviewed by the CPC, which provided additional feedback and ultimately approved it for implementation.

**STEP 2: DO**

Implementation was driven by a cross-center working group that included representation spanning the FDA. Over 4 months, the group developed a three-phase implementation strategy. Phase 1 was launched on 1 August 2016 in select offices in each center, with full implementation targeted for mid-2017. Offices that routinely receive submissions requiring cross-center consults were chosen for phase 1. Subsequent phases will engage additional center offices until all are using the new process.

The working group created materials and communications to enable successful implementation and engaged center resources to refine linkages between cross-center and center-specific processes—a crucial step, as it identified the specific individual or group in each center responsible for each stage of the process. The working group also developed and executed training to ensure appropriate knowledge transfer to users before phase 1 rollout, including how to determine whether a product meets criteria for consideration as a combination product, an overview of the new ICCR process, detailed review of the new ICCR form, and access to quick-reference tools for use during process execution. By mid-2017, most FDA staff conducting combination products review were expected to have completed this training.

**STEP 3: CHECK**

As implementation progresses, data are collected to “check” and refine the ICCR process, form, and training materials for subsequent implementation phases. Given the relatively short (2–4 months) duration of each phase and the relatively
long duration (≤12 months) of some submission reviews, data collected in phases 1–2 will focus on improvements to initial process steps. These data include: (i) number of consultations requested by center for each tier; (ii) ability to meet timeline expectations (e.g., time from application receipt to consult request; time from consult request to reviewer assignment); (iii) form usability and format (e.g., survey-driven feedback by those submitting and receiving consultations); and (iv) consult request quality (e.g., survey-based feedback focused on whether the request is clear and contains sufficient information).

Although limited data (e.g., quality; timeliness) may be available for submissions with shorter timelines in early implementation phases, a robust data set of consult completion across all submission types will not be available until the end of 2017 due to longer submission review timelines. In addition to collecting data on the ICCR process, each center will complete audits regarding combination product designation and consult tier assignment, evaluating the effectiveness of knowledge transfer for the new process and highlighting gaps for subsequent improvement. This iterative approach builds on learning from one phase to the next to ensure implementation of a robust ICCR process that enables efficient, effective collaboration.

**STEP 4: ACT**

The OCP, focal points in each center, and the CPC will monitor the ICCR process post implementation. Based on initial data collection and periodic audits, follow-up actions related to process execution and consult completion may be identified. Any additional efforts will be approved and launched through the collaboration of the centers, OCP, and CPC.

**Summary**

Positive experiences with Lean approaches at the FDA suggest potential benefits when applied to complex, multi-stakeholder processes requiring significant coordination and collaboration across multiple organizational divisions. Comprehensive assessment of Lean approaches applied to combination products review must await full implementation and evaluation of cross-center processes. However, we anticipate this flexible approach to continuous process improvement will produce efficient, effective review of combination products and offer a model for similar collaboration in medical product development and evaluation. Because combination products are regulated by different centers and subject to different statutes and regulations, the updated approach will help streamline review, prevent unnecessary delays in product clearance/approval, and make products available to patients sooner.

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