

# Investigating the Food and Drug Administration (FDA) Biotherapeutics Review and Approval Process: A Scoping Review

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## BACKGROUND

Biopharmaceutical products have become an important sector of the pharmaceutical industry in the United States (U.S.). This fast-growing sector is in a critical position in which therapeutic biological products represent over a third of all new drugs in clinical trials or awaiting approval from the U.S. Food and Drug Administration (FDA) (International Trade Administration, n.d.). The development and review of a new therapeutic biological product is a complex process that requires considerable monetary and time investment. This process takes, on average, twelve years, and the estimated average cost of taking a new drug from concept to market exceeds \$1 billion (Van Norman, 2016a). After the significant expenditure of manufacturer time and resources, many drugs fail to achieve FDA approval late in the process.

Criticism has arisen from the fact that the increasingly complex regulatory environment and expense associated with drug development have caused a lag in the release of new pharmaceuticals to the drug market. Advocacy groups and experts in the area are demanding a more rapid approval and release of new products because they consider the current process to be risk averse, slow, and inefficient (Ty Williams, 2016; Van Norman, 2016a). The FDA has created programs to expedite the approval of drugs and biological products (FDA, 2018). Despite all of these efforts, FDA scrutiny remains a long, costly, and risky process. The goal of this work is the exploration of the factors and gaps relevant to the FDA review and approval process which contribute to process inefficiencies, as well as proposed methods and solutions to address such gaps.

## REVIEW FINDINGS

Researchers who investigated the FDA review and approval operations have identified challenges and constraints in the process (e.g. Baylor, 2014; Conner et al., 2014; Kinch, 2016; Ty Williams, 2016; Van Norman, 2016a, 2016b). Van Norman (2016a) and Ty Williams (2016) emphasizes that the main challenges for the pharmaceuticals are in terms of cost and time. Complexities in the flow of information and the communications network have been identified due to the fact that the process involves multiple FDA resources and constant communication with the applicant. Additionally, complexities could arise from the review team not only having to deal with the flow of new submissions but also with the flow of resubmitted applications, which puts a strain on FDA normal operations by having to share resources between both types of submissions. Other relevant challenges are in terms of bias due to the user fees collected from sponsors and drug manufacturers to support the

drug approval process (Ty Williams, 2016) and lack of transparency of non-published drug trial data (Van Norman, 2016b).

The review of methods and solutions to address such challenges and constraints has identified a lack of research activity in studying the approval process from the regulatory agency point of view (i.e. from FDA internal operations). Most research efforts are directed toward the incorporation of modeling tools to the drugs development and production practices (e.g. Gernaey & Gani, 2010; Horner, Joshi, & Waghmare, 2017). Reform models to the current FDA review and approval process have been published with the purpose of providing flexible approaches to change the way medical products are brought to market (Thierer & Wilt, 2016; Williams, Joffe, & Slonim, 2016; Klein & Tabarrok, 2016; Conko & Madden, 2000; Gulfo, Briggeman, & Roberts, 2016). The implementation of any of these reform models may imply a shift in the responsibilities of the FDA and therefore may change the organizational structure of the regulatory agency – something that must be addressed and measured for effectiveness.

## CONCLUSIONS

Suggesting changes to the review and approval of therapeutic biological products is a challenging task. To the best of our knowledge, none of the academic articles identified in this scoping review have modeled the FDA review and approval process to address issues related to the robustness, reliability and efficiency of its operations from an internal point of view. The reform models identified in the literature are limited in several aspects. For example, there is a general lack of application of scientific methodologies and modeling techniques in understanding FDA as a complex sociotechnical system. In addition, tools and methods to assess their efficacy before implementation are largely absent.

Findings from this scoping review suggest an opportunity to employ Model-Based Systems Engineering (MBSE) approaches to provide a systems-oriented descriptive model of the FDA approval process for therapeutic biological products as a service network, with the objective of providing a method to support individual, team, and organizational decision-making to balance the process structure in terms of enforcement and information. This holistic approach will serve several investigative purposes: (1) identify influential sources of variability that cause major delays including individual, team, and organizational decision-making, (2) identify the human-system bottlenecks, (3) identify areas of opportunity for design-driven improvements, (4) study the effect of induced changes in the system, and (5) assess the robustness of the structure of the FDA approval process in terms of enforcement and information symmetry.

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