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

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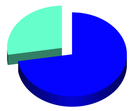
1. Background

The biopharmaceutical products have become an important sector of the pharmaceutical industry in the United States (U.S.), the country with the largest market for biopharmaceuticals (around 33% of the global market).

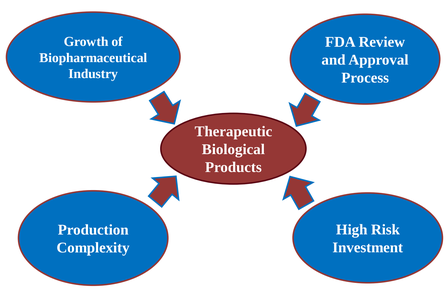
Reports from the National Science Foundation (NSF) reveal that the U.S. biopharmaceutical sector accounts for the largest single share of all the U.S. investment in Research and Development (R&D).



Therapeutic biological products represent over **one third** of all new drugs in clinical trials or awaiting for the approval from the U.S. Food and Drug Administration (FDA).

According to the FDA , a **therapeutic biological product** is a medical product made from a variety of natural sources (human, animal or microorganism) intended to treat diseases and medical conditions.

The release to market of therapeutic biological products is characterized by the following factors:



The development and review of a new therapeutic biological product is a complex process that requires considerable monetary and time investment.

The development and review takes, on average, **twelve years**, and the estimated average cost of taking a new drug from concept to market exceeds **$1 billion**.

2. Problem

- Advocacy groups and experts in the area are demanding a more rapid development, approval, and release of new products because they consider the current process to be **risk averse, slow and inefficient**; causing a lag in the release of new pharmaceuticals to the drug market.
- As an active response to critics' demands, the FDA created programs to facilitate the development and expedite the approval of drugs that treat serious conditions or fill an unmet medical need .
  - Fast Track designation
  - Priority Review designation
  - Rolling Review designation
  - Prescription Drug User Fee Act (PDUFA)
- Despite all of these efforts, the FDA scrutiny remains a long, costly, and risky process.

3. Goal

Explore 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.

4. Methods & Review Findings

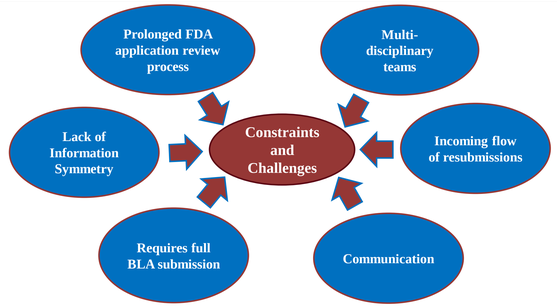
3.1 Systematic Review of Peer-Reviewed Literature

Relevant peer-reviewed journal articles, conference proceedings and official reports from public policy professional centers were reviewed.

- Inclusion criteria:
  1) Includes content about the approval of drugs and biotherapeutics
  2) Published between 2010-2017
  3) Include "cost" and "time" considerations
  4) Includes content about the operationalization of the drug review and approval process
- A total of **41 papers** met the inclusion criteria.
- Only **23 papers**, most relevant to the arguments discussed in this review, are included.

Additionally, official reports and guidelines from the FDA were retrieved.

3.2 Review and Approval of Therapeutic Biological Products



- This issues suggest the need for an assessment of the current review and approval structure.
- In addition, the need for investigating methods to **support individual, team, and organizational decision-making** to balance the process structure in terms of enforcement and information.

3.3 Modeling Approaches to the FDA Regulatory Process

3.3.1 Models and points of view

Lack of research activity in studying the approval process from the regulatory agency point of view has been noticed.

- The majority of the reviewed academic literature that modeled the FDA regulatory processes present efforts in modeling from the applicant point of view (external to the FDA internal operations).
- Few articles were found where researchers apply modeling approaches with direct application to pharmaceutical product and process design and analysis.
- Most research efforts were industry-driven and directed toward the incorporation of modeling tools to the drugs development and production practices.

3.3.2 Reform models and change management

Four models to reform the FDA approval process and change the way medical products are brought to market.

Williams et al. (2016) & Miller (2000)	Klein and Tabarrok (2016)	Conko and Madden (2000)	Gulfo et al. (2016)
Creation of nongovernmental drug-certifying bodies, changing the role of the FDA from being the "certifier of products" to being the "certifier of the certifiers"	"International Reciprocity": Allow manufacturers to market their products in the US once they have gained approval in other markets, such as the EU.	"Free-to-Choose Medicine": dual-track system which provides freedom to the patient, with the advice of their doctors, to make an informed choice of using an experimental drug.	Suggests that the FDA must re-adopt the regulation model from the 80's and 90's, where the agency is at the top of the funnel setting standards to measure drug's effectiveness based on the pharmacologic activity.

These models are limited in several aspects:

1) General lack of application of scientific methodologies and modeling techniques in understanding FDA as a complex sociotechnical system.
2) Tools and methods to assess their efficacy before implementation are largely absent.

5. Future Work

To the best of our knowledge, none of the academic articles identified in this scoping literature review have modeled the current FDA review and approval process structure to **address issues related to the robustness, reliability and efficiency of its operations from an external point of view.**

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.

Using 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
5. Assess the robustness of the structure of the FDA approval process in terms of enforcement and information symmetry

6. Implications

Adopting this approach may entail a series of limitations due to the complexity that represents **investigating internal FDA processes externally**. Modeling the approval process network just based on FDA external guidelines would not reflect the intrinsic variability in the FDA operations. As a consequence, any generated model may suffer from poor external validity.

Although this can be seen as a limitation, it also represents an opportunity for future collaboration between the FDA and academia.

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