Proposal for a Provisional FDA Designation Targeting Biomedical Products Evaluated with Novel Methodologies

Gerard Boxó Corominas Lu T. Nesterovich*

October 27, 2024

Abstract The Food and Drug Administration (FDA) is the regulatory authority responsible for overseeing food safety, pharmaceuticals, medical devices, and related products. Currently, the approval process for New Drug Applications (NDAs) and Premarket Approvals (PMAs) typically takes around 6 and 8 months [2], respectively, with a notable trend toward reduced approval times over the years. At present, the regulatory approval phase constitutes less than 10% [6] of the total drug design cycle. However, this proportion could change rapidly with the integration of artificial intelligence (AI) tools and in-silicon techniques across various phases of drug development [7], from preclinical studies to post-market monitoring.

This proposal aims to present compelling evidence supporting the potential for a significant reduction in drug development timelines in the coming years. We will also outline a rationale for a provisional exemption for certain categories of drugs and medical devices, designed to accommodate the fast pace of innovation in the biomedical field.

1 Introduction

The current drug development paradigm is a lengthy and capital-intensive process that spans several years. It involves multiple phases and various actors, starting from the initial ideation of a candidate drug and continuing through to the approval process. When we break down the development process into its components, it becomes clear that the Clinical Trial phase is the primary consumer of both time and capital.

Undergoing advancements in AI and bio-simulation promise to speed up most of the stages of drug development.

According to a Tufts report the success rate of candidate drugs, measured as the fraction of drugs that are validated in Phases I to III, sits around 12%. Current technological developments aim to dramatically increase this percentage or even render some phases dispensable.

Given that regulators have a very low baseline appetite for risk [3], we propose a Provisional Designation with a limited scope and clear guidelines for innovative drugs and medical devices. This designation would apply to products that have validation data obtained using Next Generation Clinical Trial Technology (NG-CTT). NG-CTT is an umbrella term that encompasses various advanced methodologies, including simulation, modeling, and organ-on-a-chip technologies, for assessing the safety and efficacy of biomedical products.

2 Speedups in the Drug Discovery Pipeline are Plausible in the Coming Years

Right now, a noticeable sizzle is spreading through many research laboratories in all fields, and the murmur of "What if scale and general algorithms were all we needed?" is growing louder by the moment.

*Provided valuable assistance with cross-referencing and other tasks.

Large Language Models, trained for modeling language, are now currently being used in many industries for a diversity of use cases, providing tentative evidence that scale and general algorithms can get you very far.

Motivated by this, many teams are now devising and developing a next generation of Bio Foundational models, including Structure prediction, Molecule and Protein Binding prediction and Target discovery . [4]

The impact of these new tools is still uncertain; conservative estimates predict a reduction in total time to commercialization of around 20% with the different areas of time and cost reduction widely ranging [6].

However, these numbers could very well be extremely conservative, and the final reduction could be in the ballpark of 50%.

The most relevant factors for the plausible reduction in drug development timelines are:

- Partial automation of labor-intensive processes like Literature Reviews, Basic Research, or Legal filings.
- The scaling up of the Bio Foundational models.
- Marginal decrease in compute costs.
- The in-silicon flying wheel.
- A shortening in investors' temporal preference.

By far, the factor that holds the greatest promise for reduction in Drug Development timelines is the incorporation of in-silicon Clinical Trials as partial or complete replacements for pre-clinical or clinical phases.

This, however, is still a field that raises suspicions from regulators and scientific bodies. Furthermore, it should be expected that in the near future the most capable and useful in-silicon models are data-driven, using deep learning (DL), instead of physics-based approaches, and hence the existing Risk Framework for Simulation like the V&V40 Standard [8] would not apply, further increasing regulatory uncertainties.

How should these NG-CTTs be regulated is outside the scope of this paper; we suspect, however, that comprehensive regulation is still far away and that a lot of political bargaining and advocacy are needed for these technologies to be accepted.

In this scenario, where comprehensive regulatory standards for Next Generation Clinical Trial Technologies (NG-CTTs) have yet to be established, but their use and effectiveness (through clinical surrogates) are on the rise, we propose a Provisional FDA Designation for certain novel drugs. This designation would apply to drugs that have not completed the traditional clinical phases but possess some evidence of safety and effectiveness derived from NG-CTTs.

3 Pieces of the Puzzle

The challenge we aim to address with this policy proposal is twofold. First, we anticipate the imminent introduction of AI-powered simulation tools in drug development—technologies that have yet to be fully tested. Simultaneously, we expect that advancements in current technologies leveraging deep learning (DL) will lead to increased use and effectiveness of Next Generation Clinical Trial Technologies (NG-CTTs).

To navigate the trade-offs between the commercialization of potentially life-saving drugs and the uncertainties surrounding these new methods, we propose a temporary designation designed to bridge the gap between researchers and regulators. This designation would allow the FDA time to implement in-house enabling technologies, such as generative AI and others.

Currently, the FDA has fast-tracked and special designation programs that facilitate the expedited commercialization of biomedical products under specific conditions, particularly for drugs targeting severe or life-threatening conditions. One notable example is the Breakthrough Devices Program [5].

Historically, tensions have arisen between drug companies' desire to "move fast and break things" and regulators' aversion to risk, often resulting in favor of the regulators' cautious approach. However, even if drug companies only partially transition to a faster-paced drug development model, we should expect shifts in the dynamics between drug companies and regulators, especially if the bottleneck for drug commercialization becomes a significant issue in the eyes of the public.

4 Proposal for Next Generation Clinical Trial Technologies Designation

4.1 General Requirements

The following general requirements must be met for a drug or biomedical product to qualify for the Next Generation Clinical Trial Technologies (NG-CTT) designation:

- The drug or biomedical product targets life-threatening conditions.
- Preliminary data shows a substantial improvement over available therapies.
- Preclinical and clinical data, whether obtained with in vivo lab models, human data, or through NG-CTTs, must demonstrate with reasonable confidence that the product has a good safety profile.
- The evidence for safety and effectiveness obtained through NG-CTTs will be assessed along two axes:
  - The amount of experimental data that supports the results.
  - The scientific consensus around the specific technologies used for simulation and modeling.

4.2 Implementation

This assessment could be operationalized into a scoring function based on categories and scoring points.

For example, if a concrete submission provides toxicology data with an animal model and a simulation of the toxicology in humans, the submission would score more points if it could demonstrate that the simulation accurately predicted the toxicology in the animal model (cross-species interpolation).

If a submission uses NG-CTT technology that has been published in high-impact peer-reviewed journals and has been used in other successful applications, the submission would earn additional points.

This scoring system allows for a tailored risk profile assessment that has enough flexibility to be adapted as the understanding of the underlying technologies evolves.

This initial provision for the approval of drugs and other biomedical processes could be a first approximation to a comprehensive framework for dealing with these new technologies, while minimizing current risks.

Its temporal nature should provide headroom for regulators to accommodate to new methods and processes, while also providing the needed innovation for the patients in need. Its duration should be assessed by experts, and established beforehand, with strict rules on possible extensions.

A Time and cost reductions

Main Factors for Speedup in Drug Development Timelines

The potential speedup in drug development timelines can be attributed to the following factors:

- **Partial Automation of Labor-Intensive Processes**: The drug development process is a multidisciplinary effort that requires knowledge and expertness from highly educated workers. Some of the expertise required can only be obtained trough experience in the field, for example there is no standardized way for submitting NDAs, and it's a process of trail and error plus connections. However, the potential for the automation of certain processes with already available tools is very promising, some examples of tasks that current gen AI systems could help accelerate are: literature reviews, basic research, and legal filings.
- **Scaling Up of Bio Foundational Models**: Current Bio "Foundational" models are trained with OOM less compute than current gen image or language model used by the public, while there are some uncertainties on the amount of useful data that still has not been used it's predictable that current models have a lot of headroom to get better. This development can enhance predictive accuracy and efficiency in drug discovery, leading to faster identification of viable candidates.
- **Marginal Decrease in Compute Costs**: The large computational cost of these methods made investigation and use of these kinds of models in the past, however all the forecast predict a dramatic drop in compute costs, thanks to investment in chip fabrication and rotation of inventories. These lower costs for computational resources can facilitate more extensive and faster simulations and analyses, making it economically feasible to explore more drug candidates.
- **In-Silicon Flying Wheel**: Once a single model can accurately and cheaply process/create biomedical data, a huge opportunity window appears for the creation and curation of further data leveraging the model, which produces a virtuous circle that unlocks the next level of performance for this kind of models. This has been observed in Language models and its use for data curation and distillation.

A.1 Some tentative numbers for time savings

A McKinsey report has attempted to quantify the time and cost savings associated with the use of generative AI in the drug development process. While many of the figures presented are reasonable, it is likely that even greater time savings could be realized with a more optimistic model regarding AI capability improvements.

Table 1: Time and Cost Savings for Generative AI Applications in the Pharmaceutical Industry

Application Area	Use Case	Potential Time Savings	Cost Savings
Research & Early Discovery	Knowledge Extraction	30% faster assessments	
	Compound Screening	4x faster (months to weeks)	Up to 2.5x model performance
	Drug Optimization	3x faster design	
	Indication Selection	Faster prioritization	Elimination of low-probability options
	Portfolio Optimization	10% success increase; 1-2 years faster approval	20% cost reduction
Clinical Development	Trial Co-Pilot	10-20% faster enrollment	20% cost reduction
	Data Management	50% faster data lock	30% cost reduction
	Regulatory Intelligence	30% faster responses	50% fewer follow-ups
	Submission Writing	40% faster submissions	50% cost reduction
Operations	Sourcing	50-80% productivity gain	5-10% cost reduction
	Manufacturing Assistant	15-35% less technician workload	10-15% equipment effectiveness increase
	Quality Investigations	30-40% effectiveness boost	35% productivity increase
	Inventory Optimization	20-30% workload reduction	2-3% cost reduction
Commercial	Content Creation	20% faster pipeline	30-50% cost reduction
	Review Automation	2-3x faster approvals	Improved compliance
	Enablement Co-Pilot	10-15% productivity increase	Potential 1-2% revenue growth
Medical Affairs	Insights Generation	Significant increase in insights	
	Medical Communication	50-70% faster responses	20-30% cost reduction
	Literature Summaries	2-3x engagement boost	

B Appendix B: How to enact this proposal

Navigating the legal landscape by which the proposed Temporal designation could be implemented proved to be more challenging than anticipated, and due to the limited duration of the hackathon, this aspect was left outside the scope of the report. However, a valuable starting point for understanding this process is the development of the Breakthrough Therapy designation.

The Breakthrough Therapy designation was established as part of the 2012 Food and Drug Administration Safety and Innovation Act (FDASIA). This process includes legislative action to define criteria for new designations, such as demonstrating substantial improvement over existing therapies while maintaining safety and effectiveness standards. The FDA then develops guidance documents, engaging stakeholders for input, and formalizes the designation process.

Successful case studies, such as the approval of obinutuzumab for chronic lymphocytic leukemia, illustrate the effectiveness of this approach.

References

[1] McKinsey Company, accelerating Clinical Trials to Improve Biopharma RD Productivity, 2024.

[2] McKinsey Company, Clinical development times for innovative drugs.

[3] Eliezer Yudkowsky, *Blue or Green on Regulation?*, 15 March 2007.

[4] Sarah Constantin, *AI for Bio: State Of The Field*, Rough Diamonds, 30 August 2024. Available at: `https://www.lesswrong.com/posts/CGegZveogJRGCK3LA/ai-for-bio-state-of-the-field`.

[5] Fast to first in-human: Getting new medicines to patients more quickly.

[6] McKinsey, Company, Generative AI in the pharmaceutical industry: Moving from hype to reality.

[7] Prof. Marco Viceconti, *In Silico Trials: Current Status and Future Perspectives*, Alma Mater Studiorum – University of Bologna, 2019.

[8] M. Viceconti, F. Pappalardo, B. Rodriguez, M. Horner, J. Bischoff, F. Musuamba Tshinanu, *In silico trials: Verification, validation and uncertainty quantification of predictive models used in the regulatory evaluation of biomedical products*, *Methods*, vol. 185, pp. 120-127, Jan. 2021. doi: `10.1016/j.ymeth.2020.01.011`. Epub 2020 Jan 25. PMID: 31991193; PMCID: PMC7883933.

[9] App Association, *Policy Principles for Artificial Intelligence in Health*, 2023. Available at:

[10] FDA, Successes and Opportunities in Modeling Simulation for FDA

[11] FDA Proposed Regulatory Framework for Modifications to AI/ML Based Software as a Medical Device.