IMPROVING FDA TRANSPARENCY FOR PUBLIC HEALTH

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Summary

The Food and Drug Administration (FDA) regulates the approval and marketing of pharmaceuticals and biologics. Much of the FDA's decision-making process is transparent, but not when the FDA rejects an investigational new drug filing or a new drug application. In those cases, the FDA's communications and reasoning are hidden from the public. It would improve public health, scientific innovation, and public transparency if the FDA made its communications more readily available, and Congress should amend federal law accordingly.

Challenge and Opportunity

When the FDA rejects a new drug application or an abbreviated application, it sends a "complete response letter" (or CRL) to the applicant. By regulation (21 C.F.R. § 314.110[1]), the CRL will describe all of the deficiencies in the application, such as inadequate data or a lack of efficacy. Similarly, the FDA can actually refuse to allow an application to be filed, on the grounds that it is incomplete and doesn't contain the requisite information for a full review, and will send a "refuse to file" letter (RTF).

But neither CRLs nor RTFs are made available to anyone else besides the drug sponsor. The Food, Drug and Cosmetic Act requires that safety and effectiveness data submitted to the FDA in a new drug application shall be made available to the public, unless "the application is not approvable." Under the Freedom of Information Act (FOIA), FDA regulations adopted in 1974[2] held that safety and efficacy data in FDA applications were of "enormous economic value," but that "important public policy issues . . . would be raised by disclosure of such trade secret data," and that if any change were made to require disclosure of such pre-approval information, "it should properly be made by Congress through new legislation."

The rationale for these restrictions is that the FDA's reasoning may contain confidential and proprietary information, such as trade secrets pertaining to a drug's development, manufacturing processes and intellectual property. But that often isn't true, and prioritizing this aspect over transparency comes with costs.

An analysis by Peter Lurie (then Associate Commissioner for Public Health Strategy and Analysis at FDA) and colleagues found that sponsors' press releases and other public communications rarely convey the full truth about what the FDA found as to safety, efficacy, or other data deficiencies. This analysis[3] was conducted with access to the CRLs corresponding to the press releases[4]. This problem is not limited to press releases. Academic literature is also biased towards positive results. A prominent study by Erick Turner and colleagues examined[5] FDA records and the medical literature for 12 antidepressants across 74 FDA-registered clinical trials. They found that while almost all trials with positive results were published, those negative or null results were largely unpublished or presented with a positive spin. This selective publishing led to a significant overestimation of antidepressant effectiveness in medical literature, by about 32%.

A concrete example with the problems that can arise from non-transparency involves GlaxoSmithKline's antidepressant paroxetine (Paxil). Despite FDA's rejection for adolescent use due to negative trial results, GSK published a misleading article in 2001 claiming paroxetine was effective in adolescents and successfully marketed it off-label (with more than two million prescriptions[6] in children and teens). The FDA later issued a statement refuting paroxetine's efficacy in children and adolescents, citing increased suicide risks and GSK ultimately paid a three billion dollar settlement to the federal government for false marketing of paroxetine and other drugs.

In theory, federal regulations[7] require any Phase II/III/IV trial subject to FDA approval under 21 U.S.C. § 355 to submit the trial results information to ClinicalTrials.gov, even for unapproved drugs[8]. But one fairly recent study[9] found that out of 4,209 trials, only 1,722 reported results to the website within the one-year deadline. Judging from these trends, it is quite

1 https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm?fr=314.110

2 https://www.govinfo.gov/content/pkg/FR-1974-12-24/pdf/FR-1974-12-24.pdf#page=190

3 https://www.bmj.com/content/350/bmj.h2758

4 A similar analysis to Peter Lurie et al: Harinder Singh Chahal, Sanjana Mukherjee, and Daniel W. Sigelman, "Contents of US Food and Drug Administration Refuse-to-File Letters for New Drug Applications and Efficacy Supplements and Their Public Disclosure by Applicants," JAMA Internal Medicine 181 no. 4 (2021): 522-529. (https://jamanetwork.com/journals/jamainternalmedicine/article-abstract/2775955)

5 https://www.nejm.org/doi/full/10.1056/NEJMsa065779

6 https://www.bmj.com/content/351/bmj.h4629

7 Enacted under the FDA Amendments Act of 2007, P.L. 110-85 (Sept. 27, 2007), Section 801 (amending 42 U.S.C. § 282). (https://www.govinfo.gov/content/pkg/PLAW-110publ85/pdf/PLAW-110publ85.pdf#page=82)

8 See 42 C.F.R. § 11.42. The only exception is if the company is granted a waiver for "extraordinary circumstances." 42 C.F.R. § 11.54. (https://www.ecfr.gov/current/title-42/chapter-I/subchapter-A/part-11)

9 https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(19)33220-9/abstract

unlikely that any increase in transparency, especially when it comes to negative results, will be achieved without a move towards FDA releasing appropriately redacted CRLs and RTFs.

Such a measure would be greatly beneficial to public health by providing broader access to information about rejected drug indications. This increased transparency would enhance awareness of drug safety and efficacy. Furthermore, detailed insights into FDA rejections could guide medical researchers, including those in pharmaceutical companies, away from unproductive development paths. This knowledge could be integrated into broader analyses of drug classes, optimizing future research efforts.

Moreover, this approach aligns well with the open science paradigm, which views scientific progress as a self-correcting process that benefits from maximum transparency. Given the inherently scientific nature of drug approval, increased openness in FDA decision-making could enhance the overall quality and reliability of pharmaceutical science.

It is possible that at first companies would at first object to such a move. However, we view this as a collective action problem: while it is individually disadvantageous for any one company to show negative results when others do not, across the board transparency would benefit the industry. This openness would allow pharmaceutical companies to learn from both successes and failures, potentially improving future drug applications. For instance, the FDA's recent rejection[10] of Lykos Therapeutics' application for MDMA to treat post-traumatic stress disorder (PTSD) underscores this need. Public reporting[11] has claimed that the FDA was worried about the "functional unblinding" (i.e., the patients in the control group could tell they were not receiving MDMA), but others have cited allegations of misconduct by study therapists. The broader community of drug developers would benefit from clarity around FDA's decision-making.

Since 2016, the European Medicines Agency (EMA) has provided access[12] to safety and efficacy data for all drugs, including those rejected for marketing authorization. This policy hasn't systematically disadvantaged companies seeking EMA approval, including American firms. While the FDA and EMA occasionally[13] make different decisions on identical drugs, there remains a need for greater insight into FDA decision-making.

Plan of Action

Congress should pass legislation requiring FDA to set up a Transparency 2.0 pilot, and to amend any regulations that currently require (or are interpreted to require) secrecy[14]. Because FDA has previously stated that they are unable to release CRLs and RTF letters under their interpretation of the relevant federal statutes, Congress should amend the Food, Drug, and Cosmetic Act, as well as the Defend Trade Secrets Act[15] (if necessary) to mandate that the FDA share CRLs and RTF letters, with any confidential and proprietary sensitive corporate information redacted.

FDA staff might fear the burden of redacting information from CRLs and RTFs to be very large, and in light of growing FOIA backlogs[16] across the government, which require time-consuming redaction, this is a reasonable concern. However, large language models (LLMs), like Chat-GPT and Claude, may be able to speed this process significantly. The most recent versions of such models can follow complex, multi-stage instructions, and redaction is plausibly one such type of instruction.

Given these complexities, FDA should implement this idea as a pilot that would have four stages.

Recommendation One: First, the FDA should spend six months to one year gathering input from stakeholders. For example, the FDA should:

- Gather industry input on what constitutes confidential and proprietary information, with the understanding that scientific questions (such as the safety or efficacy of a particular small molecule) are not proprietary.
- Gather researchers and societal input on what types of information are important to disclose for public health purposes.
- Report back to Congress on the results of such activities

Recommendation Two: Second, and simultaneously with the first step, the FDA should build capacity for augmented or automated redaction.

- FDA's National Center for Toxicological Research should develop benchmarks for redaction, in coordination with FDA staff who currently carry out FOIA activities. One place for such a program might be the Bioinformatics division of the FDA National Center for Toxicological Research, which has published a framework[17] for adopting LLMs.

10 https://www.nature.com/articles/d41586-024-02597-x

11 https://www.science.org/content/article/fda-advisory-panel-rejects-mdma-ptsd-treatment

12 https://www.ema.europa.eu/en/medicines/download-medicine-data

13 https://www.vbb.com/media/Insights_Newsletters/Kashoki_et_al_2019_Clinical_Pharmacology___Therapeutics.pdf

14 See 21 C.F.R. § 314.430(b) ("FDA will not publicly disclose the existence of an application or abbreviated application before an approval letter is sent . . .") ; 21 C.F.R. § 601.51 (confidentiality for biologics); 21 C.F.R. § 20.61 (defining trade secrets).

15 Defend Trade Secrets Act of 2016, S. 1890, 114th Cong. § 2 (2016).

16 https://www.gao.gov/products/gao-24-106535#summary_recommend

17 https://www.fda.gov/about-fda/nctr-research-focus-areas/artificial-intelligence

- Procure LLM software to test if that software can augment or improve the efficiency of FDA staff who currently carry out FOIA activities
- Report to Congress on the results of such activities

Recommendation Three: Third, the FDA should develop a list of initial enhanced disclosure drugs, therapeutics or devices. That is, it should develop targets for CRL and RTF disclosure, and publish this list.

Recommendation Four: Finally, the FDA should actually carry out the enhanced disclosure. In particular, it should publish the redacted CRLs and RTFs, and publish statistics on the amount of agency staff time required for such activities.

This staged rollout would allow for consideration of benefits and drawbacks of enhanced transparency, as well as continued time for LLM capability improvement and quantification. If the initial implementation was satisfactory, Congress could expand the funding and mandate of the program. At the same time, if redaction was still too time-consuming and if not enough CRLs or RTFs were actually downloaded and used, then FDA could report back on a cost-benefit analysis of continuing to make this information public.

Conclusion

With appropriate redaction, disclosure of CRLs and RTFs can improve public health without harming the legitimate business interests of the pharmaceutical industry. With new LLM tools, the FDA has the opportunity to improve transparency at a minimal burden to themselves, and also lead in responsibly incorporating AI into government.

About the Author

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