Editorial

FDA: a Disturbing Lack of Transparency

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The Food and Drug Administration (FDA) is the oldest "consumer protection agency" in our federal government.[1] It regulates biologics (e.g. blood products, vaccines, sera), drugs (for safety and efficacy), food, cosmetics, and dietary supplements (for safety), medical devices and radiation-emitting products, tobacco and related products, and veterinary products.[1]

Unfortunately, FDA has for many years lacked transparency, a deficiency that has adversely affected many aspects of science, medicine, public health, and safety. Science and medicine depend heavily on transparency, and without it, negative consequences are inevitable. In 2010, FDA noted: "The agency has been referred to as a 'black box' that makes important decisions without explaining them."[2]

According to one article, "Fraud and misconduct in clinical research is widespread."[3] The scope of the problem is very concerning: "Several studies have found that more than 40% of surveyed researchers were aware of misconduct but did not report it. Sheehan et al. reported in 2005 that 17% of surveyed authors of clinical drug trials reported that they personally knew of fabrication in research occurring over the previous 10 years."[3] FDA has uncovered evidence of fraud and fabrication in clinical drug trials for new drugs, but has routinely chosen not to make those reports available to the public.

FDA Inspection Reports Kept Hidden from Public View

A recent article highlighted the shocking scope of the problem:

> The U.S. Food and Drug Administration (FDA) inspects clinical trial sites that involve FDA-regulated products to ensure the safety of study participants and the quality and integrity of the data. These inspections occasionally reveal objectionable practices, such as failure to obtain informed consent, falsification of data, or violations in adverse event reporting…. Despite their importance, FDA inspection reports are not proactively disclosed…. FDA trial inspection reports have been largely hidden from public view.[4]

It took a Freedom of Information Act (FOIA) request to get FDA to release the concealed inspection reports. The findings in the ARISTOTLE (apixaban) and RECORD4 (rivaroxaban) trials are illustrative of the problem.

> In ARISTOTLE, a trial of the anticoagulant apixaban published in 2011, inspection visits revealed concerns with trial conduct, including fraud affecting as many as 24 of 36 sites in China. The FDA engaged in a lengthy discussion on how to address the numerous violations, noting that if data from one of the sites were excluded, the statistically significant benefit of apixaban on all-cause mortality would be lost. Ultimately, the approved labeling described the reduction in all-cause mortality associated with apixaban and did not mention data quality problems…. One study of 22 meta-analyses found that reanalysis excluding ARISTOTLE data would yield different findings in 10 (46%).[4]
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> In the RECORD4 trial of the anticoagulant rivaroxaban published in 2009, FDA site inspections identified deficiencies that affected half of the trial's 16 clinical sites, and the FDA determined that the extent of the violations warranted exclusion of the entire trial from regulatory assessment. Notwithstanding the FDA's inspection findings and actions, the RECORD4 publication does not include mention of data integrity issues and has been cited more than 1100 times by other investigators likely unaware of these issues given the lack of proactive disclosure of FDA inspection reports.[4]

Some have also studied whether clinical drug trials are ever subjected to peer review and published in the medical literature. A summary of one such study reported:

> Sim and colleagues took a rather obvious tack and went to the literature itself to look at the evidence used to support FDA approval of new drugs to see how much of it is actually published. The results, even if they overestimate the effect reported, are disturbing. It turns out that more than half of the clinical trials used to support FDA approval of drugs remain unpublished more than five years after that approval.[5]

One author also found evidence of publication bias, such that studies yielding positive results were favored over those with negative results. The author noted that publication bias "may exaggerate the advantages of new drugs over old or falsely suggest that the new drugs are more efficacious and/or safer than the old drugs."[5]

Compounding the lack of transparency is that the FDA often relies on overseas drug manufacturers, mainly in China and India, to self-monitor the quality of drugs produced and report any problems that are discovered. There have been substantial problems with generic versions of blood pressure medications, angiotensin II receptor blockers (valsartan, irbesartan and losartan) contaminated by small amounts of possible carcinogens (N-nitrosodimethlamine, N-nitrosodiethylamine).[6] Although all of the carcinogen-containing drugs were ultimately recalled, people had been taking them for some time (four years) by the time they were recalled.[7]

In a 2019 article, the director of FDA's Center for Drug Evaluation and Research stated: "People say you should go

back and inspect all of the time. Really, a lot of responsibility is on the people who manufacture and offer these drugs for sale."[8] But when is it effective for the fox to guard the chicken coop? "FDA inspectors who visited the Zhejiang Huahai Pharmaceutical factory in Linhai, China, found that workers repeatedly failed to investigate testing anomalies in drug batches. The FDA did not include the names of the drugs with anomalies in its report."[5]

Since mid-February of this year, the "fox guarding the chicken coop" approach is the only method of evaluation of drug manufactures in China since the FDA pulled all of its inspectors from China due to the risk of coronavirus infection of its workers.[9]

FDA Often Approves Drugs that Do Not Meet Its Own Uniform Guidance for Acceptable Clinical Trials

FDA also fails to disclose that it often approves drugs which do not meet its own criteria for acceptable clinical trials. One review article reported:

> Most drug candidates do not meet the strict criteria for expedited programs. For these applicants, the FDA doles out uniform guidance for acceptable clinical trials, regardless of the conditions they will treat. But a study (https://www.ncbi.nlm.nih.gov/pubmed/24449315) published in *JAMA* found that the FDA often approves drugs whose testing did not live up to its own guidance.
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> For example, the FDA recommends that drugs should be tested against control groups that take a placebo or against a similar drug already on the market. Yet more than 12 percent of new drugs the FDA approved between 2005 and 2012 did not get compared to either type of control group, according to the *JAMA* study. FDA guidelines recommend results from at least two trials that were randomized (they included control groups) and double-blind (participants were not told what kind of drug, if any, they were getting). The study's authors found that more than 63 percent of new drugs were approved on the basis of a single trial, 10 percent of trials were not randomized, and 20 percent were not double-blind.[10]

Adverse Consequences of FDA's Failure to Disclose

The adverse consequences of FDA's failure to disclose are severe and widespread. They include incorporation of poor quality, fabricated, fraudulent data into publications, meta-analyses, review articles, recommendations for "evidence-based care," clinical guidelines, formularies, and standard-of-care declarations. Failure to disclose also delays drug development, affects food safety, leads to faulty risk-benefit analyses, and ultimately to loss of credibility with the public.

An article published in April of this year includes a table detailing the adverse consequences involving two clinical trials involving data falsification and other research misconduct. They include the fact that poor quality data was cited in publications more than 6,900 times, "results were included in clinical guidelines such as that of the American Heart Association and American College of Cardiology," and the results were "included in 22 meta-analyses between 2012 and 2017." The FDA never reported these "trial irregularities."[4] The article also reported on another clinical trial where the falsified data was not retracted in a prominent publication that was cited more than 1,100 times, and was cited in numerous review articles, systematic reviews, meta-analyses, and was included in clinical guidelines of the American Association of Orthopedic Surgeons.[4]

One review article noted: "A lack of transparency in the FDA's approval process is often cited as a key source of slowdown in drug development."[10] Delays in approving effective medications can cost some their lives.

Not only does the FDA lack transparency, but the information it provides to the public may contradict information provided by another government health agency, such as the Centers for Disease Control and Prevention (CDC). In the midst of the coronavirus crisis, for instance, FDA put out stark warnings about using hydroxychloroquine to treat COVID-19 outside of the hospital setting or clinical trials.[11,12] At the same time, however, CDC had information on its website that hydroxychloroquine, which has been used safely for about 65 years, "can be prescribed to adults and children of all ages. It can also be safely taken by pregnant women and nursing mothers."[13] The CDC publication also states: "Hydroxychloroquine is a relatively well tolerated medicine. The most common adverse reactions reported are stomach pain, nausea, vomiting, and headache."[13] The side effect of torsades de pointes (TdP) due to prolongation of the QT interval by hydroxychloroquine is notably "rare."[14]

Individual risk stratification and assessment is always important, but even the American College of Cardiology concludes that the risk of arrhythmia with hydroxychloroquine "may be smaller than the potential benefit from treatment of COVID-19 for some patients."[15] The inference is that either FDA is oblivious to what information the CDC and cardiology experts are providing, or it is aware and avoids disclosing that information for some other purpose. FDA also fails to disclose important food safety information. One report noted, "FDA has jurisdiction over 80 percent of the food supply but has remained silent and opaque leaving retailers and consumers confused and at times angry at the lack of transparency."[16]

One author was perplexed by "FDA's failure to be more transparent with the public once we know the cause of the outbreak."[16] The author noted that in a food contamination case in the early 2000s (*E. coli* 0157:H7), FDA said it would reveal who manufactured the contaminated meat, but it would not tell the public the various restaurant/retailer locations where it was sold.[16] Another example of failure to disclose, was yet another *E. coli* outbreak that occurred in 2017.

> An egregious example of FDA's failure to not name retailers was 2017 *E. coli* outbreak linked to I.M. Healthy—great name for a product with a pathogen—soy nut butter that sickened dozens, some children seriously so. The outbreak began in December 2016

and reached critical mass in April 2017. A recall was publicly announced, but no retailers were named. I.M. Healthy went bankrupt and was likely uninterested or unavailable to assist in the recall. Not surprisingly, product remained available to purchase in retail settings and online several months after the outbreak and recall were announced.[16]

Failure to disclose also adversely affects clinical guidelines, causing numerous problems. Clinical guidelines are rife with conflicts of interest, and despite the word "guidelines," some have wrongfully equated the guidelines with "standard of care." In one case, failure to strictly follow clinical guidelines, contributed to a hospital-initiated sham peer review and loss of the physician's privileges. The pretext was failure to strictly follow the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines for treatment of COPD. My analysis of the 2017 GOLD guidelines found that all the GOLD board members except one (91.67%) reported conflicts of interest greater than $10,000. Pharmaceutical companies that produce medications used to treat COPD were prominently featured as the source of payments to GOLD board members. And, all (100%) of the Science Committee members of GOLD, who developed the guideline and recommendations, had financial conflicts of interest—the amount of payments they received was not disclosed. Pharmaceutical companies that produce medications used to treat COPD were again prominently featured as the source of payments to GOLD Science Committee members.

There are numerous other examples of conflict of interest impacting the development of clinical guidelines. One author noted: "A recent survey found that 71% of chairs of clinical policy committees and 90.5% of co-chairs had financial conflicts."[17]

FDA advisers also have conflicts of interest that undoubtedly influence its decisions about benefits and risks of medications. These conflicts of interest are not well-publicized. One author noted a prominent example:

> FDA advisors reviewing the safety record of the progestogen drospirenone voted that the drug's benefits outweighed any risks. However, a substantial number of the advisers had ties to the manufacturer and if their votes had been excluded the decision would have been reversed.[17]

As noted in a study published in April of this year, FDA routinely does not disclose fabricated, fraudulent data and research misconduct in clinical trials of new drugs, and those results end up being incorporated into clinical guidelines of prominent specialty societies.[4] From there, they often end up being incorporated into hospital protocols, used as a metric to evaluate physician performance, and used by insurers to make coverage decisions.[17] They become the "de facto 'standards of care.'"[17]

FDA Transparency Initiative (2010): An Abysmal Failure

Under strong criticism for its lack of transparency, and following President Obama's Open Government Initiative, FDA formed a Transparency Task Force. FDA stated:

> The Transparency Task Force is charged with seeking public input on issues related to transparency and developing recommendations for making useful and understandable information about FDA activities and decision making more readily available to the public in a timely manner and in a user-friendly format.[18]

Thus began FDA's Transparency Initiative. Details of the initiative were described in an update published in January/February 2010.[2] FDA's Transparency Initiative, unfortunately, was an abysmal failure, and the FDA persisted in its non-transparent ways.

In 2017, researchers made some specific recommendations to FDA on how to improve its transparency.[19] One summary of those recommendations described the problem:

> This lack of transparency has allowed that these processes be not only kept out of the public eye but also out of reach for the scientific community, which has caused confusion and mistrust. Although the FDA launched an initiative in 2010 called the Transparency Task Force to improve these practices, only some of their initial recommendations were adopted…. Current FDA policies have allowed for issues that have caused unease for the public and academic community, including not disclosing when a trial has been put on hold for safety reasons or when manufacturers have released misleading information about a product.[20]

Just as one can lead a horse to water but cannot make it drink, one can make recommendations to FDA to improve transparency, but one cannot force it to adopt and implement them.

Shocking Report by Former FDA Inspector

Taking lack of transparency to the extreme, an NBC News interview with a former FDA inspector revealed that critical safety recommendations of its own inspector were overruled by FDA officials.

> The valsartan recall came as little surprise to Massoud Motamed, a former inspector with the U.S. Food and Drug Administration (FDA). More than a year before the notices went out, Motamed had tried to sound the alarm on what he flagged as potential systematic problems at two facilities in China and India that produce the active ingredients in generic valsartan and other blood pressure medications.
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> Speaking publicly for the first time, Motamed told NBC News that the FDA ultimately overruled his recommendation to crack down on one of the plants. Perhaps more alarming, he says the issues at the two overseas drug production facilities are hardly unique. "This is just the tip of the iceberg…. I believe it would surprise Americans how much we rely on the manufacturer and whatever they tell us to say that a drug is good or bad."[7]

Severe quality problems were not limited to China. When the former FDA inspector reviewed closed-circuit TV footage

at one drug manufacturing plant in India he found:

> …individuals shredding company documents four days before his arrival.... "They were staying up all night shredding extensive amounts of documents right before our audit." …Some 19 months after Motamed first flagged suspicious activity at the plant, Hetero [production facility] was found to be one of the sources of the contaminated drug ingredients for sale in the U.S.[7]

Although FDA found that the tainted medication contained up to 210 times the agency's acceptable level for the carcinogen NDMA, it downplayed the risks: "The FDA says the overall risk posed by the impurities is small."[7]

Conclusion

Transparency serves the best interests of patients, the general public, physicians, and the scientific community. The FDA has a demonstrated history of being highly resistant to both internal and external efforts to improve transparency. The FDA, a government agency tasked with evaluating medications, food, and other products/devices has an obligation to proactively inform the public about safety issues in a timely manner.

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