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FDA oversight of clinical trials is "grossly inadequate," say experts

Covid-19 vaccines and drugs were developed at "warp speed" and now experts are concerned that the US Food and Drug Administration inspected too few clinical trial sites. Maryanne Demasi reports

Maryanne Demasi *investigative journalist*

On 25 September 2020, the US Food and Drug Administration (FDA) received a complaint by Brook Jackson who had been working for Ventavia Research Group, a Texas based company hired to run clinical trials for Pfizer's covid-19 mRNA vaccine. Jackson, a regional director, had witnessed problems at three trial sites she was overseeing and complained to an FDA inspector about a range of problems including falsified data, unblinded patients, and inadequately trained vaccinators who were slow to follow up on adverse events. "I thought that the FDA was going to swoop in and take care of everything. What I was reporting was so important," Jackson told *The BMJ*. The FDA did not, however, inspect the trial sites in question.

This lack of oversight was not an isolated case, *The BMJ* has learnt. Regulatory documents show that only nine out of 153 Pfizer trial sites[1] were subject to FDA inspection before licensing the mRNA vaccine. Similarly, only 10 out of 99 Moderna trial sites[2] and five of 73 remdesivir trial sites[3] were inspected.

Now, facing a backlog of site inspections, experts have criticised the FDA's oversight of clinical trials, describing it as "grossly inadequate." They say the problem, which predated covid-19, is not limited to a lack of inspections but also includes failing to notify the public or scientific journals when violations are identified—effectively keeping scientific misconduct from the medical establishment.

The FDA is "endangering public health" by not being candid about violations that are uncovered during clinical trial site inspections, says David Gortler, a pharmacist and pharmacologist who worked as an FDA medical reviewer between 2007 and 2011 and was then appointed as a senior adviser to the FDA commissioner in 2019-21.

"The lack of full transparency and data sharing does not allow physicians and other medical scientists to confirm the data independently and make comprehensive risk-benefit assessments," continues Gortler, who is now a fellow at the Ethics and Public Policy Center thinktank in Washington DC.

Paused during the pandemic

Between March and July 2020, at the peak of pandemic restrictions, the FDA paused its site inspections and only "mission critical" inspections were carried out. Gortler says, however, that this was the time that the FDA should have ramped up its oversight, not scaled back, especially since covid-19 products were being developed at warp speed and intended for millions of people. "The drug companies took appropriate measures to keep staff safe, which is exactly what the FDA could and should have done," said Gortler.

A former staffer in the FDA's Office of Criminal Investigations was also concerned about the agency's failure to fully tackle Jackson's complaint about falsified data in Pfizer's mRNA vaccine trial. In an email dated March 2021, they wrote, "Having worked at the FDA, I see it as surprising, for many reasons, that the agency turned a blind eye . . . They likely feared the criticism they undoubtedly would have received for holding up a vaccine (which they knew they would eventually approve anyway) at the expense of untold lives lost."

The former FDA employee, who signed a non-disclosure agreement and did not respond to interview requests, went on to write, "My point here is that instead of the regulators protecting the public, they were complicit. At the time, they may have been doing what they believed to be the right thing under extraordinary circumstances. But now, they may soon have some explaining to do."

The FDA told *The BMJ* it takes oversight of clinical trials seriously and had adapted to travel restrictions, publishing draft guidance[4] for remote regulatory assessments. This guidance describes virtual inspections using live streaming and video conferencing and requests to view records remotely.

Gortler, who is a credentialed FDA inspector, laughed at the proposition. "You can't do a remote inspection. That's like saying I'm going to arrest somebody remotely. You have to be there on site and look at every nuance such as cleanliness, organisation, staff coordination—even their body language. During a pandemic, the FDA could've put inspectors in hazmat suits if they wanted to, there's no excuse for not going onsite."

Historical failure to oversee

The FDA has a long history of failing adequately to oversee clinical trial sites. A report in 2007 by the Department of Health and Human Services' Office of the Inspector General found the FDA audited less than 1% of the nation's clinical trial sites between 2000 and 2005[5] and was highly critical of the agency because it did not have a database of operational clinical trial sites.[6] In response to the report, the FDA said it created a dedicated task force and "developed new regulations and guidance further to improve the conduct of clinical trials and enhance the protection

of people participating in clinical trials." *The BMJ* asked to interview a member of this task force, but the FDA denied our request.

In 2015, Charles Seife, professor of journalism at New York University, conducted an analysis of published clinical trials between 1998 and 2013 in which an FDA inspection found significant evidence of objectionable practices.[7] A total of 57 published clinical trials had significant evidence of one or more problems: 39% had falsification or submission of false information, 25% had problems with adverse events reporting, 74% had protocol violations, 61% had inadequate or inaccurate recordkeeping, and 53% failed to protect the safety of patients or had problems with oversight or informed consent. Furthermore, only 4% of the trials that were found to have significant violations were mentioned in the study's journal publications.

A 2020 *Science* investigation analysed the FDA's enforcement of clinical research regulations between 2008 and 2019 and concluded the agency was often light handed, slow moving, and secretive. It said that the FDA rarely levelled sanctions and when it did formally warn researchers about breaking the law, it often neglected to ensure that the problems were remedied.[8]

It has been 15 years since the Office of Inspector General report and the FDA still has no record of how many clinical trial sites are operating across the US and abroad. The agency told *The BMJ* it does not compile an annual list of clinical investigational sites submitted for review because it is "resource intensive."

"It's unacceptable," said Gortler. "All it would take is sending a blanket communication to all sponsors or applicants requesting they provide a list of all their international and domestic clinical trial sites. Also, the FDA should publish the names, inspection dates, and unredacted findings at each of these sites clearly on its website, not buried somewhere, nearly impossible to find." He believes the agency should have implemented a policy decades ago. "The public has a right to learn immediately about any violations before choosing to use an FDA regulated product," he says.

Some 65% of the FDA's funding for the evaluation of drugs comes from industry user fees and in return the agency has mandated deadlines for decisions on new product applications. Some experts argue this has been a major contributor to the FDA being rushed and having insufficient resources for other critical activities.[9]

Insufficient staff and low morale

Historically, the FDA has faced challenges recruiting and retaining sufficient medical staff to meet its needs. According to a Government Accountability Office report published in January 2022, the turnover rate for FDA staff in key scientific areas was twice that of other government agencies in 2007, leaving the agency unable to fulfil its mission.[10] Around 70% of the FDA's career employees working in 2008 were eligible to retire by the end of 2014. Moreover, in 2018, medical product staff in "mission critical" occupations had salaries that were at least 20% lower than the average private sector salary for the same occupations, contributing to low morale. A news report said the pressures of work during the pandemic had led to two FDA reviewers dying by suicide.[11]

Despite the estimated hundreds of thousands of clinical trial sites in operation across the US and abroad, the FDA told *The BMJ* that it only has 89 inspectors for its bioresearch monitoring programme, which assure the quality and integrity of data submitted to the agency in support of new product approvals and marketing applications. The FDA told *The BMJ* it is recruiting more inspectors to reach its yearly average of 100.

"I don't think that it is a sufficient number of staff to do that kind of level of oversight," says Jill Fisher, professor of social medicine at the University of North Carolina. "The FDA must have enough of a presence to dissuade investigative sites from committing fraud," she continues.

Secrecy of inspection findings

Occasionally, the FDA will uncover objectionable practices, such as failure to obtain informed consent, falsification of data, or violations in adverse event reporting.

The FDA publishes its inspection reports[12] but the database is not comprehensive, nor are the reports proactively disclosed. When they are disclosed there can be extensive redactions making it difficult to link problems to a particular drug or clinical trial. "FDA redactions can render the document useless—it's to the point of being comical," says Gortler, whose current work focuses on FDA oversight and accountability. "Public health information should not be redacted like that," he says.

The FDA does not typically notify journals when a site participating in a published clinical trial receives a serious warning, or alert the public about the research misconduct it finds.[13]

Rafael Dal-Ré, physician epidemiologist at the Health Research Institute-Fundación Jiménez Díaz University Hospital, Madrid, Spain, finds this concerning[14] and points to the example of the anticoagulant drug rivaroxaban.

The FDA inspected trial sites of the Record 4 trial and identified serious deficiencies at eight of the study's 16 trial sites.[14] The violations were so numerous and severe that the FDA excluded the trial from its pile of evidence during the drug's approval. But when the study was published in the *Lancet* in 2009[15] there was no mention of the data integrity problems and the paper has been cited more than 1100 times by others.[14] When *The BMJ* sought comment from the authors of the Record 4 study, some said they were not fully aware of the data integrity problems prior to our inquiries. The lead author, Alexander Turpin, said he was seeking more information from the drug company. The *Lancet* told *The BMJ* it was looking into the matter.

"If research misconduct is identified, the FDA may reject the affected data from the product's safety and efficacy evaluations, but then fail to disclose these data in the product labelling," added Dal-Ré.

Gortler finds it unconscionable that the FDA withholds this information from the public. "Misconduct should be released immediately. It's malpractice not to; it's irresponsible," he says.

In response to the criticism the FDA said that it does not always monitor all publications of data that were submitted to the agency, nor does it have the authority to demand that a journal retract an article.

Road to reform

Fisher says the FDA needs better resourcing. "The clinical trials industry has become a complex global enterprise, and the FDA does not have the resources to oversee all the research that is happening, even within the US. The FDA needs to be better funded and staffed to conduct inspections. At a minimum the agency needs to inspect sites when complaints or concerns have been filed," she says.

Gortler doesn't agree, however, that the FDA is under-resourced. With a total budget of $6.1bn in 2021, he suggests the agency needs to be leaner and more efficient, with employees interested in improving public health. "The bottom line is that the FDA has over 18 000 full time employees, more than any other drug regulatory

agency by far, so it could have retrained and retooled anybody to tackle the need for increased inspections," he says. "Half of its budget, about $3bn, is discretionary, which means it could have hired contractors, retirees, or repurpose existing workers. It chose not to. The FDA was just yawning its way through the pandemic. The entire agency is broken."

"It felt like we were being told to hide things": FDA's approval of antibiotic Ketek

In 2004, the FDA approved Sanofi-Aventis's new antibiotic Ketek (telithromycin) for outpatient treatment of community acquired respiratory tract infections. Since then, it has been implicated in hundreds of reported cases of severe liver injury and dozens of deaths, triggered two Congressional hearings, and led to reforms of the agency's processes. In 2007, the FDA added a warning to Ketek's label and removed all indications except for bacterial pneumonia.

David Ross was an FDA medical reviewer who led the initial safety review for Ketek in 2001, as part of a 10 year career at the agency's Center for Drug Evaluation and Research. In his original review Ross, now an associate clinical professor of medicine at George Washington University School of Medicine and Health Sciences, found that Ketek's risks included liver injury and other serious adverse events that were concerning given the millions of antibiotic prescriptions written annually for respiratory tract infections.[16]

In 2001, the FDA recommended to Sanofi-Aventis that the company gather additional safety data. Sanofi-Aventis conducted Study 3014, a 24 000 patient safety study done in only five months. The FDA's limited resources only allowed one out of 1800 sites to be inspected initially.

The agency decided to inspect the highest enrolling site, reasoning that failure to find any problems there would allow all the other sites to be considered clean. "The FDA inspector found evidence of blatant fraud almost immediately. For example, patients being enrolled at times when the clinic was supposedly closed," said Ross.

The inspector reported her findings to FDA's Office of Criminal Investigations, with serious protocol violations subsequently found at several other high enrolling sites. Eventually, the site investigator pleaded guilty to fraud and served a 57 month prison sentence.

At a 2003 public meeting of the FDA's anti-infective advisory committee, data from Study 3014 were presented to the panel without disclosing the numerous violations and data integrity problems found at the initial trial site, which sparked a criminal investigation. Janice Soreth, Ross's division supervisor at the time, has previously said that there was no intention to deceive the committee and that the violations were not disclosed so as not to compromise the ongoing criminal investigation.[17] But Ross says he was appalled: "I felt like we were being told to hide things from the advisory committee."

Unaware of the integrity problems, the committee voted 11 to 1 to recommend approval of Ketek. The FDA granted the drug approval on 1 April 2004. In a memorandum from the FDA, the agency said it was "difficult" to rely on Study 3014 for its approval because of the data integrity problems, instead using spontaneous adverse events reports for its understanding of Ketek's overall risk-benefit profile, which goes against standard drug review practice.[18] The first Ketek associated death from liver injury was reported to the FDA seven months later.[16]

A series of events unfolded during the drug approval process, which would later be revealed at a Congressional hearing in 2007. Ross testified under oath that when he submitted his follow up safety review in 2004, concluding that Ketek carried far too much risk to ever be approved for relatively minor conditions such as bronchitis and sinusitis, Soreth asked him to "soften" the language so that it would give the leadership "more wiggle room." He told the hearing he sent Soreth a revised version for signing but—without telling her—also put the original in the electronic archive. Soreth did not testify in the hearing and denies this allegation. "No one ordered a change in Dr Ross's review. He was free to keep his original draft," she told *The BMJ*. "His review, moreover, did not include Aventis's final submission to the agency."

Ross left the division after Ketek's approval in 2004 and then left the FDA in 2006, saying "the FDA did nothing for months and they just watched as the adverse event reports piled up. Lives could and would have been saved if the FDA acted sooner than it did to publicise Ketek's risks and put a boxed warning on the drug."

Whether it was Ross or Soreth who was right about this, the Ketek controversy led to the FDA Amendments Act of 2007, which stated that a reviewer's work "shall not be altered by management or the reviewer once final."

The FDA declined to respond when contacted by *The BMJ*. A spokesperson for Sanofi said the company complied with all the investigations at the time and that it no longer sells Ketek.

Competing interests: I have read and understood BMJ policy on declaration of interests and have no relevant interests to declare.

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1 FDA. Summary basis for regulatory action: Comirnaty. 2021. www.fda.gov/media/151733/download.
2 FDA. Summary basis for regulatory action: Spikevax. 2022. www.fda.gov/media/155931/download.
3 FDA Center for Drug Evaluation and Research. Summary review: other relevant regulatory issues. 2020. www.accessdata.fda.gov/drugsatfda_docs/nda/2020/214787Orig1s000SumR.pdf#page=29
4 FDA. Conducting remote regulatory assessments: draft guidance for industry. July 2022. www.fda.gov/media/160173/download.
5 FDA Department of Health and Human Services. The Food and Drug Administration's oversight of clinical trials. 2007. www.oig.hhs.gov/oei/reports/oei-01-06-00160.pdf.
6 Tanne JH. FDA is failing to oversee human clinical trials, report says. *BMJ* 2007;335:. doi: 10.1136/bmj.39356.358796.DB pmid: 17916839
7 Seife C. Research misconduct identified by the US Food and Drug Administration: out of sight, out of mind, out of the peer-reviewed literature. *JAMA Intern Med* 2015;175:-77. doi: 10.1001/jamainternmed.2014.7774 pmid: 25664866
8 Piller C. Official inaction. 1 October 2020. www.science.org/content/article/fda-s-own-documents-reveal-agency-s-lax-slow-and-secretive-oversight-clinical-research.
9 Demasi M. From FDA to MHRA: are drug regulators for hire? *BMJ* 2022;377:. doi: 10.1136/bmj.o1538 pmid: 35768073
10 US Government Accountability Office. FDA workforce: agency-wide workforce planning needed to ensure medical product staff meet current and future needs. 2022. www.gao.gov/assets/gao-22-104791.pdf.
11 Eban K. "A tsunami of randoms": how Trump's covid chaos drowned the FDA in junk science. Vanity Fair. 19 January 2021. www.vanityfair.com/news/2021/01/how-trumps-covid-chaos-drowned-the-fda-in-junk-science.
12 FDA. Inspection observations. www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/inspection-references/inspection-observations.
13 Doshi P, Godlee F. The wider role of regulatory scientists. *BMJ* 2017;357:. doi: 10.1136/bmj.j1991 pmid: 28450290
14 Dal-Ré R, Kesselheim AS, Bourgeois FT. Increasing access to FDA inspection reports on irregularities and misconduct in clinical trials. *JAMA* 2020;323:-4. doi: 10.1001/jama.2020.1631 pmid: 32324205
15 Turpie AGG, Lassen MR, Davidson BL, etalRECORD4 Investigators. Rivaroxaban versus enoxaparin for thromboprophylaxis after total knee arthroplasty (RECORD4): a randomised trial. *Lancet* 2009;373:-80. doi: 10.1016/S0140-6736(09)60734-0 pmid: 19411100
16 Ross DB. The FDA and the case of Ketek. *N Engl J Med* 2007;356:-4. doi: 10.1056/NEJMp078032 pmid: 17442902
17 Soreth J, Cox E, Kweder S, Jenkins J, Galson S. Ketek--the FDA perspective. *N Engl J Med* 2007;356:-6. doi: 10.1056/NEJMc076135 pmid: 17442912
18 Graham DJ. Telithromycin and acute liver failure. *N Engl J Med* 2006;355:-1. doi: 10.1056/NEJMc066372 pmid: 17124030