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COMMENTARY

The decline of science at the FDA has become unmanageable

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Before 1962, US federal law did not require pre-marketing proof of effectiveness for drugs. But senate hearings revealing widespread false advertising of drugs—along with the thalidomide safety disaster—spurred Congress into action. From then on, approval of a New Drug Application (NDA) by the US Food and Drug Administration required proof of "substantial evidence" of effectiveness. This proof was defined as results from "adequate and well-controlled investigations, including clinical investigations,"[1] with such evidence also required to advertise claims of safety and effectiveness. A National Academy of Sciences review underscored the need for these mandates, finding over 30% of pre-1962 marketed drugs to be ineffective.[2]

The FDA's legally enforceable regulations detail what "substantial evidence" and "adequate and well-controlled investigations" mean in greater depth, supplemented by guidelines to industry which, although not legally binding, explain the FDA's current interpretation of drug manufacturers' legal obligations.[3] However imperfect, the FDA's enforcement of these provisions assures prescribers, patients, and payors that effectiveness claims are based on science, not science fiction. A published FDA review showed efficacy deficiencies, in whole or in part, underlying initial rejection of 89 of 151 NDAs (59%), highlighting the continuing need for vigilance on this front.[4]

However, as Peter Doshi reports in *The BMJ*,[5] the FDA subverted the legal standard for effectiveness in its 2019 approval of Recarbrio, a fixed dose combination of imipenem, cilastatin, and relebactam. While the FDA has previously approved products with marginal evidence of effectiveness,[6] approval of the Recarbrio NDA was shocking given its lack of substantial evidence of effectiveness and the complete absence of adequate and well controlled clinical investigations on the actual indication of interest.

Despite these egregious breaches of legal and regulatory standards, FDA officials declared substantial evidence to be present, citing animal and laboratory studies. However, federal law and the FDA's own regulations allow adequate and well controlled non-clinical studies to serve as substantial evidence only when adequate and well controlled clinical studies are neither feasible nor ethical, which was not the case with Recarbrio.[7]

The Recarbrio approval is even more troubling because of other inexplicable departures from fundamental scientific, regulatory, and procedural principles. These included the failure to require "that each active component [of a fixed dose combination drug] contributes to the effect claimed for the product."[8] The FDA's conclusion that Recarbrio at best does not reduce the efficacy of an approved drug can hardly be considered a demonstration that a component "contributes to the effect claimed for the product." In addition, office directors responsible for approval decisions are required to provide "a rationale for concurrence or non-concurrence with the review team and the division director."[9] For Recarbrio, however, the "reviews" by both the office director and the division director responsible for its approval consist of nine words: "I concur with the review team's assessment and recommendations."

Finally, despite all the NDA's defects, the FDA decided not to present it to an FDA advisory committee, as called for by law,[10] on the basis of an astonishing statement that "there were no controversial issues that would benefit from advisory committee discussion." The absence of adequate and well controlled clinical investigations in an NDA would normally cause the FDA to find the application to be unapprovable on its face and to refuse to even review it.[11] Incredibly, the FDA granted Recarbrio a priority review, shortening the time to approval by 40%. Even more incredibly, the FDA designated Recarbrio as qualifying for financial incentives aimed at encouraging development of drugs to treat infections caused by resistant organisms—despite the lack of substantial evidence that Recarbrio does actually treat such infections.[12]

Scientific culture

What accounts for this descent into cargo cult science? Much of the blame must go to the FDA's reliance on industry paid user fees. Over the past three decades the proportion of the FDA's annual drug budget made up of such fees has risen from less than 10% (fiscal year 1994) to more than two thirds (fiscal year 2023).[13 14] In addition, the alluring "regulatory flexibilities" provided by the FDA Modernization Act of 1997 and the 21st Century Cures Act have become habit forming, enabling the FDA's leadership and managers to deny scientific reality by defining effectiveness downward. In its quest to avoid difficult choices and hard decisions the FDA has increasingly embraced non-inferiority trials (or vice versa), ignoring the serious regulatory, clinical, and ethical problems caused by their misuse.[15]

However, the corruption of the FDA's scientific culture remains the primary culprit driving the deterioration of safety and effectiveness standards. During my tenure at FDA, managers would admiringly speak of "crafting an approval," as if it were a skilful demonstration of regulatory legerdemain rather than an act of scientific fabrication. The Recarbrio approval illustrates that

the situation has, if anything, worsened since then. FDA leadership's continued hostility towards meaningful peer review, transparency, and accountability dims the prospect for institutional self-renewal. So has the failure of much touted internal pathways for disagreement, which have amounted to little more than virtue signalling.[16]

Transparency

What can be done about this dismal situation? The first step is admitting that there's a problem—that the decline of science at the FDA has become unmanageable. Fifteen years ago, in a trenchant essay, Peter Barton Hutt, chief counsel for the FDA from 1971 to 1975, wrote that "science at the [FDA] today is in a precarious position" and that "the agency is barely hanging on by its fingertips."[17] Warning that user fees had damaged FDA science and credibility while simultaneously disguising the damage, he called on Congress to adequately fund the FDA. Although politically fraught, tapering the FDA's dependence on user fees would involve less than 0.2% of the annual federal budget. This would be a small price to pay for checking the continuing corrosion of the agency's scientific integrity by user fees.

The second—and more achievable—step requires improving public access to the information received by the FDA, its reasoning, and its decisions. In addition to enabling meaningful peer review and engagement by providers, patients, researchers, healthcare organisations, and drug manufacturers with the FDA on the scientific basis for its actions, increased transparency would highlight the FDA's value as a producer of information.[18] Fifty years ago the agency issued regulations providing broad authority to disclose safety and effectiveness data.[19] Subsequently, however, the FDA reinterpreted its authority under the Freedom of Information Act to significantly narrow the scope of information it would release.[20] Its continuing refusal to disclose non-trade secret information, such as the effectiveness data in the Recarbrio NDA, is untenable given the FDA's existing authorities[21] and its ability to implement congressionally mandated transparency reforms, such as the requirement to post NDA action packages to the FDA's website within 30 days of approval, without having to promulgate new regulations.[10]

The Recarbrio approval is a sentinel event, warning of a return to an era when drug effectiveness was an afterthought. Although the FDA crowed about this approval,[12] it would have been better advised to remember that "for a successful technology, reality must take precedence over public relations, for nature cannot be fooled."[22]

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