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Experts' Views on FDA Regulatory Standards for Drug and High-Risk Medical Devices: Implications for Patient Care

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BACKGROUND: Drugs and high-risk medical devices are increasingly likely to receive Food and Drug Administration (FDA) approval through expedited pathways, which has implications for informed treatment consent (i.e., consent in clinical practice).

OBJECTIVE: To obtain expert opinion about the clinical and ethical implications of the increasing availability of new drugs and devices approved through expedited development and regulatory review pathways.

DESIGN: Qualitative study using individual semi-structured videoconference interviews.

PARTICIPANTS: National leaders in medicine, ethics, and law (n=12) with expertise in medical product regulation, payor policymaking, bioethics, physician practice, patient advocacy, public health expertise/advocacy, clinical trials, the pharmaceutical and device industry, institutional review board oversight, and real-world evidence.

MAIN MEASURES: Principal themes in 3 domains: expedited regulatory pathways, physician and patient understanding of and reliance on FDA approval, and informed treatment consent.

KEY RESULTS: Respondents pointed out that more common use of expedited pathways translates to increased reliance on surrogate measures, some with uncertain clinical significance. While expedited development and review can have advantages, participants expressed worry that physicians were unaware when medical products were expedited and did not communicate about uncertainties in knowledge about new drug or device approvals effectively with patients. Many participants felt that informed treatment consent discussions about new drugs or devices should include some explanations of expedited pathways and use of surrogate measures.

CONCLUSIONS: Experts identified advantages of expediting development and of FDA flexibility in applying its standards to new drugs and medical devices, but highlighted concerns that patients may not be adequately informed about the risks of shorter review times or about uncertainties in the evidence that result. There is a need to identify approaches to ensure effective clinical use of drugs and devices when approved through expedited pathways.

KEY WORDS: FDA regulatory standards; expedited approval; informed consent.

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INTRODUCTION

The U.S. Food and Drug Administration (FDA) evaluates the safety and effectiveness of new drugs and medical devices before they are approved for marketing. Since the 1980s, numerous formal pathways have been created that aim to shorten clinical development and regulatory review times, and a growing number of drugs and devices enter the market via these expedited pathways.[1–3] Most recently, in 2012 and 2016, Congress established "Breakthrough" designations for drugs[4,5] and medical devices[6–8] to shorten the clinical testing process, such as by enabling approvals for promising products based on trials that are "as efficient and flexible as practicable, when scientifically appropriate".[9] Expedited testing makes new treatments more rapidly available to patients, but collecting less pre-approval safety and effectiveness data also places greater importance on post-approval evidence generation.[1]

There are limited data about the extent to which physicians and patients are aware of details about regulatory evaluation of drugs and devices. In surveys, more than 90% of physicians reported that they trust that FDA approval of drugs means benefits outweigh risks for approved indications,[10] although they may be unaware of what indications have FDA approval.[11] While nearly 80% of physicians think that drugs should be approved based on at least 2 randomized trials,[10] the share of newly approved drugs supported by 2 or more efficacy trials decreased from 81% in 1995–1997 to 53% in 2015–2017.[3] High-risk medical devices are even less likely to be tested in more than one prospective randomized trial.[12–14]

If physicians are unaware of evidence supporting drugs and medical devices, they will be unable to communicate such information to patients. Patient consent to treatment following clinician disclosure of risks and benefits is the ethical cornerstone of clinical care. However, the extent to which uncertainty about evidence must be disclosed is unclear. Arguably, the nature of informed treatment consent should vary based on the quantity and quality of the clinical data supporting a new medical product,[15] but there is no consensus on how informed treatment consent should be adapted when products receive expedited regulatory review. To help understand the regulatory, clinical, and ethical implications of these issues, we conducted semi-structured interviews with 12 national leaders in medicine, ethics, and law.

METHODS

Expert Recruitment

Using purposive sampling, we conducted 1-hour, semi-structured interviews with experts about the speed of new drug and device testing and approval and the implications for evidence generation and informed treatment consent. Invitees had national reputations—achieved through academic publications, government service, and/or leadership roles in patient-focused organizations or the private sector—in at least one of the following: medical product regulation, payor policymaking, bioethics, physician practice, patient advocacy, public health expertise/advocacy, clinical trials, the pharmaceutical and medical device industry, institutional review board oversight, and real-world evidence. Real-world evidence refers to information on health care derived from sources outside of typical clinical research settings, such as electronic health records, health insurance claims records, product and disease registries, and data from personal digital devices.[16–18] We conducted individual interviews, as opposed to using a group setting, to allow each expert the opportunity to share detailed views on the current state of drug and device development and regulation without the influence of other individuals or perspectives. Individuals were invited by email and offered a $500 honorarium. Institutional Review Board approval was obtained at the University of California, San Francisco and Brigham and Women's Hospital.

Semi-structured Interview Guide and Interviews

We wrote a semi-structured interview guide covering three domains (**Appendix Material**). The first domain addressed FDA approval of drugs and high-risk medical devices, including how expedited regulatory pathways balance pre- and post-approval evidence generation and how they have changed over time. The second domain covered physician and patient understanding of and reliance on FDA approval. The third domain covered physician-patient communication preceding informed treatment consent for recently approved drugs and high-risk medical devices. The interview guide was piloted and revised based on an interview with an expert physician-bioethicist.

Interviews were conducted via videoconference between January and April 2020 by at least two members of the research team using the interview guide, although interviewers had authority to ask points of clarification. Interviews were recorded and transcribed.

Qualitative Analysis

Two investigators (SSD and JJD) independently reviewed an initial set of 3 randomly selected transcripts and categorized each line of text as addressing a particular topic and subtopic (e.g., "evidence: surrogate endpoints"). Through an iterative approach, a codebook classification system of topics and subtopics was generated (**Table in Appendix**). Once the codebook was developed, all transcripts were independently coded by one of the two reviewers. Our analysis focused on describing themes that emerged from the group, but themes were not always unanimous, as individual experts at times had different perspectives on the material.

Role of the Funding Source

The Greenwall Foundation Making a Difference grant program had no involvement in the design of the study; the collection, analysis, and interpretation of the data; and the decision to approve publication of the finished manuscript.

RESULTS

Participants

Of 13 national experts invited to participate, 12 accepted (Table 1), most of whom had multiple areas of expertise. Three had expertise in medical product regulation, one in payor policymaking, four in bioethics, four as physicians, one in patient advocacy, two in public health expertise/advocacy, two in clinical trials, two in institutional review boards, and one in real-world evidence. The themes are discussed below, along with additional representative quotes (Table 2).

Interview Theme 1: FDA Approval

Evidence Supporting New Drug and Device Approval Varies and Has Changed Over Time. There was consensus that the evidence supporting approval of new drugs was more extensive than those for high-risk devices and that the standard that the FDA applied to that evidence in evaluating drugs was neither too high nor too low. As one participant stated, "the drug approval process has worked pretty well in terms of getting drugs that are generally pretty good approved…"

However, most participants felt that the FDA has in recent years lowered the bar for evidence it accepts for new drugs and devices. One stated, "What we've seen over the past probably two decades is an erosion of the application of that standard

Table 1 Expert Participant Names, Affiliations, and Expertise

Name	Affiliation	Expertise
Michael Carome, MD	Public Citizen	Physician, institutional review boards, public health expertise/advocacy
Neal Dickert Jr, MD, PhD	Emory University School of Medicine	Physician, bioethics
Nancy Dreyer, PhD, MPH	Chief Scientific Officer, IQVIA Real-World Solutions	Real-world evidence
Holly Fernandez Lynch, JD, MBE	University of Pennsylvania Perelman School of Medicine	Bioethics, medical product regulation
Jill Fisher, PhD	University of North Carolina, Chapel Hill	Bioethics, clinical trials
Michelle Mello, JD, PhD, MPhil	Stanford University School of Medicine	Bioethics, institutional review boards
Casey Quinlan	Mighty Casey Media	Patient advocacy
Alan Rosenberg, MD	Former Vice President of Medical and Pharmacy Policy, Anthem	Physician, payor policymaking
Robert W. Yeh, MD, MSc	Beth Israel Deaconess Medical Center, FDA Special Government Employee	Physician, clinical trials
Diana Zuckerman, PhD	National Center for Health Research	Public health expertise/advocacy
Anonymous	Former government official	Medical product regulation
Anonymous	Former government official	Medical product regulation

Abbreviation: FDA Food and Drug Administration

(safety and effectiveness), even though the language continues to exist in the statute and in the regulations," and another said, "I think there's a common opinion among academic circles that ... the bar is lower." The examples most often cited in support of these perceptions related to therapies for rare diseases and genetically defined subtypes of cancer that received approval through expedited pathways based on single-arm trials with surrogate endpoints and historical controls (rather than randomized, blinded trials with active controls).

Respondents noted that expedited pathways bring some helpful medical products to patients with diseases that may not have available therapies. As one respondent said, "The impetus to have accelerated pathways is a good one…if you are dealing with a disease that doesn't have a lot of therapeutic options available to patients, there are really good reasons to do that." Respondents also discussed the benefits to for-profit manufacturers in reduced time and cost to bring a drug or medical device to market.

An expressed concern was that these pathways were being overused, "Companies are able to take advantage of those quicker ways to get FDA approval for products that aren't particularly novel or in areas that they're not as needed...the execution of it has been more in favor of the market as opposed to the practice of medicine." Many respondents expressed worry that some products using these pathways may not serve patients well because of underlying uncertainty about safety and efficacy, "It's safe enough, efficacious enough to be put on the market, but…not that we have really good knowledge about how safe it is and what kinds of adverse events are really going to be created over the long term when millions of people might be taking a product."

Use of Surrogate Measures. Surrogate measures were noted as being used more often than in the past. One respondent thought that surrogate measures were necessary because endpoints showing clinical benefit can sometimes be too costly. For example, respondents noted that oncology trials would be longer and therefore more expensive for the sponsor if the endpoint was survival. Respondents noted that surrogate measures could be helpful when correlated to clinical outcomes.

Some respondents also cited multiple examples of drugs approved based on trials showing changes to surrogate endpoints that were later found to not have clinical benefit, such as

Table 2 Illustrative Remarks for Each of the Identified Themes

Themes	Illustrative remarks
FDA Approval: Evidence Supporting New Drug and Device Approval and Change Over Time	"There is this process over time of making it easier for products to get on the market and creating a perception that the standards haven't shifted, when in fact, they have pretty dramatically."
FDA Approval: Use of Surrogate Measures	"More and more the outcomes are biomarkers or surrogate endpoints that are not really proven to make a difference in people's health or quality of life."
FDA Approval: Post-market Evidence Generation	"The incentive to do really properly conducted trials—after the device is already approved? It's so low."
Physician and Patient Understanding and Views of FDA Processes	"Most physicians and maybe just about all patients, except for scientists, don't understand the lack of certainty about the safety and effectiveness of the medical product that the FDA has approved."
Informed Treatment Consent	"[L]ay audiences...look at me like I have three heads...: 'But it was approved. What do you mean it's not going to work for me or might not work for me?'"

Abbreviation: FDA Food and Drug Administration

bevacizumab for metastatic breast cancer. Some mentioned drugs for which the surrogates were unlikely to translate to clinical benefit; eteplirsen (Exondys 51), approved in 2016 for Duchenne muscular dystrophy, was mentioned by multiple respondents.

Some respondents said that, while surrogate measures have potential to shorten length of trials, it was important to validate surrogates as clinically meaningful. One participant stated, "I think we would all love to have good ones, but good ones are very hard to find." Another stated, "The problem is using unvalidated surrogates as though they were validated and treating them forevermore as though they were validated."

Post-market Evidence Generation. Participants discussed reliance on post-market evaluation strategies to address uncertainties remaining at the time of regulatory approval. They pointed out that FDA can, and does, mandate post-market safety and effectiveness studies, require adverse event reporting, and leverage real-world data.

Participants noted that required post-market studies were not always completed and were not timely for many reasons, such as slow enrollment. As one remarked, "If we don't get it (production of evidence) pre-approval, it's obviously quite difficult to get it post-approval." Some respondents indicated that drug or device companies have few incentives to complete post-market trials, "Right now we have a system where if they've met that bar, the incentive to do really properly conducted trials—after the device is already approved? It's so low." Some participants suggested that the FDA do more to ensure post-marketing study completion: "They've not been aggressive in pushing companies and enforcing penalties when…[there is] failure to complete a trial." Another noted the difficulty in rescinding approval when the company had not completed a mandatory post-market trial.

Limitations of adverse event reporting, such as underreporting, were also noted: "It's not always done. It's sort of at the discretion of the provider to fill something out." Some participants also noted the need to know the denominator for adverse event reports.

Finally, registries, electronic health records, and insurance claims data were all felt to be inexpensive ways to generate post-market evidence. Some respondents mentioned Medicare's Coverage with Evidence Development (CED), which requires data entry to receive reimbursement. However, one respondent expressed concern that "In a lot of treatments… you're looking for endpoints that you're probably not going to find in real world data," such as quality of life indicators. Another gap was lack of integration of the unique device identifier (UDI) into electronic data systems to facilitate tracking of medical devices. Another respondent noted a need for development of reliable analytic methods to enable real-world comparative effectiveness research.

Interview Theme 2: Physician and Patient Understanding and Views of FDA Approval

Participants all felt that physicians and patients trusted FDA approval but had limited understanding of the specifics of the approval process. One respondent stated, "I think many doctors and patients believe if it's FDA-approved, it must be safe and it must be effective." Explanations for physician perceptions were lack of inclusion of regulatory issues in medical education and training. One participant stated, "Both evidence interpretation as well as what it means to be approved—we didn't learn this at all in medical school."

Respondents doubted that many physicians independently reviewed or were aware of the nature and limitations of the evidence supporting approval of the new drugs or devices. Participants noted that FDA review documents were time-consuming to peruse, if physicians were even aware that these documents were available. Respondents believed physicians were more likely to learn about evidence supporting drug and device approval through conferences, peer-reviewed publications, industry detailing, and their colleagues. Respondents noted that industry-supported information is widely available, but often not appropriately balanced.

With respect to patient understanding, one participant expressed concern that use of some terms related to expedited approval pathways, such as the "Breakthrough" designation, would confuse patients: "I worry actually that that might convey exactly the wrong kind of information to patients. That it would actually convey that it's something superior for clinical use when that's not at all what it means."

Interview Theme 3: Informed Treatment Consent

Some respondents believed that consent to the use of drugs and devices should be preceded by a presentation of information to the patient about the underlying evidence supporting its expected effects, with more details offered about newer therapies.

Some respondents noted variability in the process of obtaining informed treatment consent, with physician-patient conversations often limited in substantive content about safety and effectiveness, "The consent process is largely one that fulfills the bare minimum legal requirement right now." Some participants identified the usual dynamic as one in which a physician would "write the prescription and say 'You should take this.'" Some respondents perceived that treatment consent conversations did not often cover the quality and quantity of evidence supporting a drug or medical device being used in their care. Some also noted that physicians may minimize information about harms, as exemplified by this quote: "Physicians are worried particularly about talking about side effects and risks of drugs because they're concerned that a patient will forego a treatment that really is in their best interest." Because high-risk medical devices usually involve procedures, participants

thought treatment consent in these situations was more detailed. A few respondents expressed concern about the timing of treatment consent discussions, which often occurred after a patient had arrived for an elective procedure, instead of earlier, when decision-making about the course of care took place.

Some participants thought that informed treatment consent discussions should include information about approval pathways and surrogate measures, "Accelerated approval… There's no clear clinical benefit. It's based on a surrogate endpoint. I would think it would be something that might be relevant for the patient to understand." However, some respondents also worried about how physicians would express uncertainty, "Uncertainty is really challenging because patients don't like to hear that physicians feel uncertainty. Often I think they perceive uncertainty on the part of the physician as incompetence, even though it's just an actual reflection of the reality." Instead, physicians may even emphasize new therapies, with one respondent saying that physicians might tell patients, "It's a new drug, very promising."

DISCUSSION

A group of national leaders in medicine and law reflecting on recent trends in FDA approval for new drugs and devices expressed concern over whether physicians are aware of evolving application of basic evidentiary standards and how details of approvals and lingering uncertainty about risks and benefits are communicated to patients. These findings raise important ethical concerns about patient decision-making and the current state of drug and device regulation in the USA.

Some participants noted that approval standards for drugs have generally been adequate, and reviews show that in the last decade about one-third of new drugs in the USA are rated by international health technology assessment bodies (the Human Drug Advisory Panel in Canada, the Ministry of Health in France, the Federal Joint Committee in Germany, the Italian Medicines Agency in Italy, and the non-profit organization, Prescrire) as offering moderate or better improvement over available treatments.[19] Many participants also saw potential benefits to the use of surrogate measures and expedited approval pathways, which allowed lower clinical trial expenses for the sponsor and faster market entry. This could be advantageous for life-saying treatments, especially for diseases with no available effective therapies.

However, many experts in this study were concerned about cases in which regulatory approval of new products was granted based on trials lacking the well-established hallmarks of rigorous evidence, such as randomization, blinding,[2,5,7] and showing changes to questionable surrogate measures,[5,7,20–22] as highlighted by the recent approval of aducanumab (Aduhelm)® for Alzheimer's disease based upon reduction in amyloid plaques (a controversial decision that occurred after our interviews were completed).[23,24] Such characteristics translate to greater uncertainty about the benefits and risks of a product and have been linked to increased safety-related label changes,[25–27] recalls,[28] and withdrawal of some drug indications from the market for failure to confirm efficacy.[29] Vulnerable populations may be affected; for example, multiple devices authorized through the Breakthrough Devices Program in recent years are intended to treat diseases usually experienced by older adults, such as advanced heart failure and severe emphysema.[7]

Post-market studies were cited as being essential to filling gaps in the evidence generated prior to approval. However, FDA may not always require post-marking studies.[7,30–32] Many experts also worried about low rates of post-market study completion and reporting and about the fact that completed studies may take many years to produce data.[14,32–35] Although some participants mentioned potential for real-world data to provide complementary information, they also noted limitations that have been described in the literature, including a need to validate the outcomes of studies that use real-world data.[36–38] Real-world data for medical devices were noted by respondents to be limited given the lack of integration of the UDI into electronic data systems and claims.[39,40] Additionally, the observational nature of real-world data may limit causal inference[22,41] and allow multiple analyses with only the positive ones reported; therefore, there is a need to ensure that these studies are registered and their results are reported in a timely manner.[42] Finally, using routine clinical care experiences to evaluate unproven medical products raises ethical questions, since patients in clinical care do not routinely provide informed consent for their data to be used for generalizable research.[15]

Experts' concerns that physicians may not communicate clearly the level of uncertainty that comes with most new drug and device approvals highlights opportunities for improvements. For physicians to fulfill the ethical imperative of adequately explaining information about risks and benefits to their patients, they must first acquire this knowledge themselves. However, prior research has found that physicians have limited understanding of statistical methods, bias in studies, and relevance and validity of evidence.[43] They tend to overestimate benefits and underestimate harms,[44] including of drugs approved under the Breakthrough Therapy Designation.[45] Despite these limitations in physician understanding of benefits and risks, physicians rarely communicate uncertainty to patients.[46] Our findings suggest that these issues are exacerbated in the context of more expedited medical product approvals.

Patients may trust when even suboptimal information is shared by physicians because patients generally have limited independent understanding of clinical research[47]— but trust that FDA ensures the safety and effectiveness of medical products and that physicians are well-informed about benefits, risks, and uncertainty.[48] For example, if a patient group, perhaps funded by industry,[49,50] pushes for approval of a drug with objectively small or questionable benefits, physicians may truthfully communicate that the drug has recently received FDA approval, that it received "priority review" or other special

treatment such as approval with the Breakthrough Therapy Designation,[4,5,51] or perhaps that it is the only drug approved to treat a particular condition. Despite physician or payor skepticism of the drug's therapeutic value, it may be confusing to a patient to learn that the FDA-approved drug likely provides small or uncertain benefit, making it difficult to obtain truly informed treatment consent from the patient. One FDA approval having some of these characteristics was that of eteplirsen (Exondys 51) for Duchenne muscular dystrophy.[52] Despite receiving priority review, fast-track status, and accelerated approval, the drug showed minimal effectiveness against a surrogate endpoint.[52] Mandated post-approval evidence has not been generated while patients continue to receive eteplirsen, and other new drugs in the class have received similar expedited approvals.[22]

In this context, our findings about lack of patient knowledge of features of expedited approval pathways could further compromise patient autonomy and the ability to make informed decisions.[15] The recent approval of aducanumab will test if many physician-patient discussions include information about the uncertainty of evidence and required post-approval trials.[23]

One solution would be to shift the focus from unmet need, which is a criterion for the major expedited approval pathways, to instead focus on the extent to which drugs satisfy that need. For example, new legislation could limit the use of certain expedited pathways unless the benefits of a drug or device in early testing appear to be large compared to standard-of-care treatments.[53] Second, aligning incentives might be needed to ensure completion of post-market studies, such as legislation requiring time-limited approvals or required FDA re-examination of all drugs and devices approved via expedited pathways after a certain number of years.[54] Third, clinicians should be better educated about FDA regulatory pathways and approval standards as well as strategies for communicating uncertainty to patients in undergraduate, graduate, and continuing medical education. Fourth, available information about product risks, benefits, and uncertainties, including underlying data when appropriate, should be made more readily available to patients before the patient arrives at the pharmacy counter or for a procedure. Though prescribers are primarily responsible for such communication, doing so can be difficult in time-constrained clinical practice settings, and regulators could help by making key information more readily available and understandable.

Our study should be considered in the context of multiple limitations. First, we conducted an in-depth qualitative study of twelve purposively sampled respondents. While they are national experts, they may not be representative of physicians, ethicists, or regulatory experts as a whole and our approach of conducting separate interviews did not allow a determination of consensus on any point. Second, inclusion of additional representatives from other fields (e.g., drug or device companies, payors, general internists or family physicians) may have provided further insights. Third, responses may have been influenced by social desirability bias, with participants replying in ways expected to be considered favorable instead of their true views.

CONCLUSION

Twelve experts in medicine, ethics, and the law reported various considerations related to expedited testing and approval of new drugs and medical devices and how to improve the communication to patients of the limits of the evidence on which these products were approved.

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Declarations:

Conflict of Interest: *Dr. Kesselheim served on the FDA Peripheral and Central Nervous System Advisory Committee from 2015-2021, and voted against the approval of eteplirsen (Exondys 51).*

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