



What's in Your Medicine Cabinet?

Ensuring the Safety and Efficacy of Prescription Drugs,
Biologics and Medical Devices in the United States

A Policy Paper

By the

Yale Collaboration for Research Integrity and Transparency

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This policy paper was developed and written by the faculty and staff of the Collaboration for Research Integrity & Transparency (CRIT) at Yale University. It was edited by Margaret E. McCarthy (Executive Director, CRIT) and Gregg Gonsalves (Assistant Professor, Yale School of Public Health).

About the CRIT Program

The Collaboration for Research Integrity and Transparency (CRIT) is an interdisciplinary initiative launched in 2016 at Yale to enhance the quality and transparency of the research base for medical products. Through research, advocacy, and litigation, CRIT is focused on ensuring that the clinical evidence that supports and informs our understanding of the safety and effectiveness of pharmaceuticals, medical devices, and other medical products is accurate, comprehensive, accessible, and reliable.

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Executive Summary

With the start of a new presidential administration in 2017, a new commissioner of the Food and Drug Administration (FDA), Dr. Scott Gottlieb, was appointed, replacing Dr. Robert Califf who had served in this role since 2015. Dr. Gottlieb's tenure began on the heels of the enactment of a major piece of legislation affecting the agency—the 21st Century Cures Act—and on the cusp of approval of another major bill, the Food and Drug Administration (FDA) Reauthorization Act of 2017. In the midst of these changes, it is an opportune time to reflect on the FDA's historic mandate to ensure the medical products used by all Americans are safe and effective, and offer recommendations to the new Commissioner, the new Administration and Congress to strengthen this vital public health institution.

In this policy paper, the Collaboration for Research Integrity and Transparency, a joint program of Yale Law School, Yale School of Medicine and Yale School of Public Health, offers an analysis of the challenges currently facing the FDA in seven areas:

1. Pre-market regulation of new medical products;
2. Post-market follow-up of medical products;
3. Pre-approval access to experimental therapies;
4. Use of real-world evidence;
5. Off-label marketing;
6. Regulation of medical devices, and;
7. Enhancing access to clinical trial data, including patient level data, summary level data and meta-data.

The recommendations in each of these areas are laid out below, while the full report provides the analytic framework from which these recommendations were derived.

The goal of these recommendations and this report is to promote health by improving the integrity and transparency of biomedical and clinical research, and improving the underlying evidence supporting the efficacy and safety of medical products regulated by the FDA.

SUMMARY RECOMMENDATIONS

1. Strengthen Pre-Market Regulation of New Medical Products

- Before implementing broader use of surrogate markers as primary endpoints in clinical trials supporting medical product approval, the FDA should convene an advisory committee to examine the current expedited pathways for medical product approval, including an examination of the appropriate use of surrogate markers.
- The FDA should convene an expert panel to conduct a review of all existing drugs and biologics approved for use and made available in the U.S. as a result of an expedited approval pathway, including those approved on the basis surrogate endpoint markers, to determine if they are safe and effective.
- If drugs and biologics approved through expedited pathways are not found to be safe and effective by the expert panel, the FDA should recommend manufacturer withdrawal of these agents, either for the indication for which evidence suggests lack of safety or efficacy or for the product as a whole.
- If indications or products are withdrawn, FDA should communicate with doctors, patient groups, standard setting organizations, and insurers to better inform them of the reasons for the withdrawal.

2. Secure Adequate Post-Market Follow-Up of Medical Products

- Congress should provide adequate funding and staffing for the FDA to monitor compliance with requirements for post-market studies, as these activities are not adequately supported by the Prescription Drug Users Fee Act.
- The FDA should convene an expert panel to examine the use of fines and other existing penalties for failure to complete post marketing studies, to examine their effectiveness in compelling compliance by companies, and to suggest additional mechanisms to ensure timely completion of post-marketing requirements.
- Congress should enact new legislation that requires manufacturers to enroll patient subgroups traditionally underrepresented in medical research, including the elderly, women, and racial and ethnic minorities, in similar proportions to disease prevalence, in post-market trials, to strengthen the generalizability of results, beyond the narrow pre-market study patient populations.
- Congress should enact legislation that gives the FDA authority to order a drug recall, similar to its existing recall authority over food, medical devices and biologics.

3. Improve Access to Experimental Therapies Through Expanded Access Programs

- Congress should enact legislation that requires study of the current barriers to expanded access to experimental treatments, and reporting on recommendations for needed change.

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- Congress should not enact legislation that circumvents the FDA's oversight over expanded access to experimental treatment, or that cedes authority over access to experimental treatment to the states.

4. Avoid Low Quality, Real-World Evidence

- The FDA should clearly and concretely define the term “real-world evidence” in all contexts to exclude data from single arm trials, trials using historical controls, non-representative patient surveys, case reports, and patient testimonials. The FDA should include data from prospectively planned interventions, interventions that collect data on clinical endpoints, and pragmatic trials in the definition of real world evidence.
- Even though the 21st Century Cures Act excludes randomized studies from the category of “real-world evidence,” the FDA should make clear that prospective, randomized and controlled clinical trials cannot be replaced as part of pre-market evaluation, and substituted with lower quality data. While real-world evidence may complement the information learned from these trials, it cannot reliably replace it.

5. Resist Efforts to Weaken Off-Label Marketing Restrictions

- The FDA should not revise its current rules or guidelines to permit drug companies to engage in more communications about off-label uses than are currently permitted. The draft FDA guidance documents released in early 2017 should be adopted as final guidance documents.
- The FDA and the U.S. Department of Justice (DOJ) should continue to prosecute cases of off-label promotion, and commit to fully litigating the First Amendment issue.

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- The FDA and DOJ should be transparent regarding their approach in enforcing restrictions on off-label marketing, including how they litigate off-label cases, settle them, and negotiate with pharmaceutical companies.

6. Strengthen Regulation of Medical Devices

- The FDA should convene an expert panel to recommend legislative changes to provide an updated framework for regulation of Class II devices that accounts for safety and effectiveness across the device lifecycle, as recommended by the Institute of Medicine.
- The FDA should strengthen its current regulatory requirements for clinical trial data for evaluating pre-market applications for Class III devices. In addition, FDA should evaluate industry compliance with post-marketing requirements, including the establishment of tracking systems, reporting of device malfunctions, serious injuries or deaths, post-market surveillance studies as well as post-approval studies required at the time of approval of a pre-market approval (PMA).
- The FDA should enforce the requirement that all medical devices are labeled with a unique device identifier and that all health plans and federal payers, including the Centers for Medicare and Medicaid Services, modify their standard administrative claims billing file to include a data element for the unique device identifier.

7. Improve Access to Clinical Trial Data, Including Patient Level Data, Summary Level Data and Meta-Data

- Congress should enact legislation requiring disclosure to public health, clinical, and basic science researchers of all clinical trial data provided to the FDA as a

condition of approval. Data disclosed should include summary-level data, meta-data, and de-identified patient-level data, including case reports.

- The DOJ should implement a policy requiring sharing of legacy and future clinical trial data by pharmaceutical companies, including summary-level data, meta-data, and de-identified patient-level data, as a condition of settlement in cases brought against pharmaceutical companies.
- The FDA should enforce existing reporting requirements for registering and reporting results for completed clinical trials through the National Institute of Health's public clinical trial registry, [ClinicalTrials.gov](https://clinicaltrials.gov).
- Congress should enact legislation requiring that clinical trial data from post-market studies provided to the FDA, including summary-level data, meta-data and de-identified patient-level data, be made available in an easily accessible manner to researchers.
- The FDA should adopt all of the recommendations of the FDA Transparency Working Group.

Introduction

Today's Food and Drug Administration (FDA) is a product of a series of American tragedies: contamination of vaccines at the turn of the 20th century; dangerous substances found in commonly sold medicines in the 1900s; deaths of over 100 children and adults in 1937 from a sulfa drug dissolved in diethylene glycol (antifreeze); extensive birth defects caused by thalidomide in the early 1960s; and infertility and deaths caused by the Dalkon Shield intrauterine device in the 1970s.¹ Concern regarding the risk of unsafe medical products led to the enactment of the Food, Drug and Cosmetic Act in 1938, which required that manufacturers submit safety information for new drugs to the FDA, with a two month review period before drugs could be sold. But the 1938 law still allowed unsafe products to reach the market, and there was no review for effectiveness. Additional concerns regarding unsafe and ineffective medical products led to the passage of the Kefauver Harris Amendments of 1962 and the Medical Device Amendments of 1976 to the Food, Drug, and Cosmetic Act. These laws established, among many other regulatory responsibilities, the requirement that manufacturers conduct adequate and well-controlled studies, demonstrating safety and efficacy before drugs and biologics are approved for use, and established government oversight of medical devices, along with many other related animal and consumer products.

Despite these tragedies, some opposed the changes enshrined in the Kefauver-Harris amendments, claiming that new regulatory requirements for the approval of medical products would impede the development of new drugs by the pharmaceutical industry.² Pressure from patient groups, particularly HIV/AIDS activists, led to the creation of new mechanisms to provide expanded access to new treatments prior to approval.³ Documented delays in drug approval in the 1970's and 1980's, due in part to lack of staffing, led to changes at the FDA, including the enactment of the Prescription

Drug User Fee Act in 1992, which provided a new funding mechanism for additional staff to review applications for new medical products. These changes sped access to medical products, making the agency one of the fastest drug regulators in the world, reviewing new drug or biologic licensing applications more quickly than regulators in the European Union and Canada.^{4,5} Today, the FDA is consistently the first regulatory agency in the world to approve new therapies for use.^{4,5} Recent FDA data indicate that ninety-five percent of new molecular entities submitted under a New Drug Application or Biologic License Application are approved.^{6,7} The FDA's current regulatory requirements, necessitating adequate and well-controlled studies that demonstrate safety and efficacy, prior to approval of drugs and biologics, lower the risk that products that are unsafe or ineffective will reach the market, while addressing the need for timely approval and patient access for new products.⁸

The transition to a new administration and the recent passage of the 21st Century Cures Act, make this an opportune time to step back and reflect on the FDA's competing obligations. The FDA is charged not only with protecting public health and assuring patient safety, but also with conducting rapid evaluation of new medical products so that patients can receive safe and effective new treatments in a timely manner. The 21st Century Cures Act contains provisions that could be interpreted to further diminish the agency's role, depending on the nature of implementing regulations and guidance documents. There is pressure on the agency to go further, either on its own or failing that, through additional legislative or judicial action, to further speed approval or reduce evidentiary requirements.^{9,10} Such action may endanger the public health.¹¹ While an innovation gap in pharmaceutical research and development currently exists, there is no evidence to suggest that regulatory demands are the cause of this putative shortfall.^{12,13} The misguided quest to further diminish the perceived regulatory burden imposed by the agency places not only the FDA's role in

protection of public health, but also the credibility of its review process of medical products at risk.^{14,15}

We believe that concerted attention is necessary to preserve and even strengthen the FDA's ability to ensure that drugs, biologics and medical devices are safe and effective. We oppose proposals to lower evidentiary requirements for approval and marketing of new drugs and biologics and post-market review of medical devices. We also oppose allowing companies to make broader claims about new uses for products that are already on the market, in absence of FDA approval of these new uses.¹¹ This would lead to an erosion of the current safeguards put in place to protect patients from unsafe and ineffective medical products and risk eroding the reputation of the agency and the pharmaceutical and device industries in turn that depend on credible and rigorous oversight by the FDA.

We draw these conclusions based on our analysis of the FDA's mandate and regulatory structure and scholarly research that has examined how FDA has performed in this context, as well as the various proposals to change the underlying regulatory framework for the evaluation of medical products in the US. We have identified seven key areas where new policies, funding or legislation are urgently needed to ensure that medical products used by patients in the US continue to be safe and effective. In particular, we provide solutions to address concerns related to:

1. pre-market regulation of new medical products;
2. post-market follow-up of medical products;
3. pre-approval access to experimental therapies;
4. use of real-world evidence;
5. off-label marketing;
6. regulation of medical devices, and;
7. enhancing access to clinical trial data, including patient level data, summary level data and meta-data.

1. Improve Pre-Market Regulation of New Medical Products

Problem	Current expedited pathways for FDA approval may result in regulatory approval of medical products before benefits or harms are adequately studied.
Solution	The pre-market approval processes at the FDA should be strengthened to increase the evidence base for the safety and efficacy of drugs, biologics and high-risk devices approved under expedited pathways.

The FDA offers several expedited programs for approval of drugs and biologics for serious and life-threatening conditions. The number of drugs approved via these pathways grows every year.¹⁶ Regulatory procedures to expedite approval were first established in 1988 for HIV/AIDS drugs, and were hailed by many as an important step to address the lack of approved therapies and to reduce the thousands of deaths from HIV/AIDS. Since 1988, the categories for expedited approval have expanded. Currently, drugs may qualify for accelerated approval, breakthrough designation, fast track, and priority review—pathways that enable the FDA to consider approving drugs for serious unmet medical needs more quickly. With regard to devices, the FDA has an expedited access program as well as a breakthrough therapy designation.

The current expedited processes can result in premature approval of inadequately proven drugs and biologics. Use of accelerated approval and breakthrough therapy designation means that widely variable—and sometimes less rigorous—pre-market data is gathered regarding the efficacy and safety of drugs and biologics approved for serious conditions.¹⁷ Nearly all drugs granted accelerated approval are approved based on a surrogate marker (a stand-in for a clinical endpoint,

such as a blood cholesterol level standing in for heart disease, or a clinical endpoint other than mortality or irreversible morbidity).¹⁷

Although the use of surrogate markers for trial endpoints was initially hailed as a lifesaving change to clinical evaluation requirements, enabling shorter and smaller clinical trials, a growing body of evidence indicates that surrogate endpoints may not accurately predict the health outcomes for which they stand in.^{17,18} A recent systematic review examined published post-market studies of drugs approved by the FDA between 2005 and 2012 on the basis of limited evidence. The review revealed that for drugs approved on the basis of surrogate markers, that less than one-tenth of those drugs had a published peer-reviewed post-market study establishing that the drug was effective based on clinical evidence.¹⁹ Similar findings have been made in studies examining post-market peer-reviewed publications in cardiology and oncology for drugs approved on the basis of surrogate endpoints.^{20,21}

Furthermore, drugs approved through an accelerated approval pathway are granted conditional approval only with the requirement that evidence of clinical efficacy be confirmed after this initial approval. This allows the FDA to withdraw the conditional approval if post-marketing studies fail to show efficacy. This rarely happens.²² There is one notable example. In 2008, Avastin (bevacizumab) had been granted accelerated approval to treat HER-2 negative metastatic breast cancer, and approval was conditioned on demonstration of efficacy demonstrated through post-market studies.²³ In 2011, the FDA withdrew approval for Avastin for breast cancer treatment after post-market studies failed to demonstrate efficacy.²³ However, Avastin remained on the market for other approved uses, and 60% of medical providers in oncology, surveyed subsequent to the December 2010 announcement of the Avastin withdrawal for breast cancer treatment, indicated that they would continue to prescribe Avastin off-label to patients with breast cancer for the revoked indication.²⁴ Thus, even

in the case where FDA has withdrawn approval, once a drug is on the market, controlling its use, even the absence of evidence that it is effective for an indication, is difficult. Rigorous pre-market evaluation of new products is essential—it is the place in the lifecycle of a drug where the incentives for producing evidence of safety and effectiveness of new products are the strongest.

Evidence from two recent surveys of patients and doctors suggests that patients and health care providers do not understand that medical products that go through an accelerated pathway may be on the market before benefits or harms have been adequately studied, and that they may have only conditional approval. The breakthrough therapy designation, for example, is one form of accelerated approval. A drug or biologic is eligible for breakthrough designation if it is intended to treat a "serious or life-threatening disease or condition and preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over existing therapies on 1 or more clinically significant endpoints such as substantial treatment effects observed early in clinical development."²⁵ A recent survey of board-certified internists and specialists physicians found that the majority misinterpreted the term "breakthrough," with more than ninety percent indicating that they would choose a hypothetical new drug with breakthrough designation over an existing treatment.²⁶ A survey of patients revealed a similar misunderstanding, with patients significantly more likely to rate a new treatment described as promising or breakthrough as "very effective" or "completely effective" than a new treatment that was not described in those terms.^{27,28} The results of these studies suggest that patients may refrain from using better-studied drugs if their doctors—whose knowledge of drugs is necessarily limited by the sheer scope of literature they have to review to stay up to date in their field²⁹—are unaware that a new drug has received only conditional approval.

The 21st Century Cures Act includes a provision requiring the Health and Human Services Secretary to qualify drug development tools, like surrogate markers, that can be used to gain approval of drugs or biologics. This provision provides an opportunity for a re-evaluation of the relative usefulness of surrogate markers, the establishment of a pathway to validate these markers in terms of their ability to predict clinical benefit, and a strengthening of the agency's ability to ensure that drug approvals based on these surrogates are validated with clinical endpoints in the post-marketing environment.

Recommendations

Before implementing broader use of surrogate markers, the FDA should convene an advisory committee to examine the current expedited pathways for medical product approval, including an examination of the appropriate use of surrogate markers as primary endpoints in clinical trials supporting medical product approval.

The FDA should convene an expert panel to conduct a review of all existing drugs and biologics approved for use and made available in the U.S. as a result of an expedited approval pathway, including the evidence base for surrogate endpoint markers used in the approval process, to determine if they are safe and effective.

If drugs and biologics approved through expedited pathways are not found to be safe and effective by the expert panel, the FDA should recommend manufacturer withdrawal of these agents, either for the indication for which evidence suggests lack of safety or efficacy or for the product as a whole.

If indications or products are withdrawn, FDA should communicate with doctors, patient groups, standard setting organizations, and insurers to better inform them of the reasons for the withdrawal.

2. Secure Adequate Post-Market Follow-Up of Medical Products

Problem	Data from post-market studies and surveillance can provide key information on medical product safety and efficacy. Yet many post-market studies for new medical products are delayed or not completed, leaving patients, health care providers, and insurers with partial information on their safety and effectiveness.
Solution	The Secretary of the Department of Health and Human Services (HHS) should use all enforcement mechanisms at the department's disposal to ensure compliance with rigorous post-marketing studies of new medical products.

When new drugs and biologics are approved, the evidence supporting their approval is limited by the short time frame of studies, and the limited population exposed to the new drug or biologic in clinical trials. Pre-approval clinical trials for chronic illnesses rarely measure long-term effects, with only 9% of drugs approved for chronic diseases supported by at least one clinical trial of a year's duration, making post-market studies all the more crucial.¹⁷ Pre-market studies typically involve a narrower patient population than the market for the approved medical product. Clinical trials have exclusion criteria that limit who can enroll as a participant. These typically include age, disease progression, co-occurring conditions, and pregnancy or breastfeeding. Historically, U.S. clinical trials have not included adequate numbers of women, people of color, the elderly, and many vulnerable or marginalized populations. Despite the requirement in the National Institutes of Health Revitalization Act of 1993 for inclusion of women and members of racial and ethnic minority populations in NIH-funded trials, this underrepresentation continues.³⁰⁻³² Some populations not considered

in the initial approval are included in follow-up studies. Although the Pediatric Research Equity Act requires studies in children for many medical products, these are regularly conducted after approval as part of post-market requirements. Post-market studies, as well as adverse event reports submitted to the FDA through the Adverse Event Reporting System or the mini-Sentinel project, may reveal important positive or negative effects of the medical product that were not evident in the original data that led to approval.

Safety issues involving newly approved drugs and biologics are common. A recent study of novel drugs and biologics approved by the FDA between 2001 and 2010 found that 32% were affected by a post-market safety event (withdrawal due to safety reasons, issuance of boxed warning, or FDA issued safety-communication). The median time from approval to first post-market safety event was 4.2 years, indicating that adequate post-market surveillance is key to identifying safety issues after approval.³³ The FDA needs additional financial resources to adequately track and respond to safety issues in the post-market context.³⁴ Although 5,000 staff positions at the FDA are currently funded by manufacturer fees under the user fee acts, these staff members review applications and pre-market notifications for new medical products, and are only responsible for enforcing post-market safety, but not efficacy, requirements.³⁵

The FDA currently has inadequate resources available to enforce post-market requirements, despite the fact that many required post-market studies are not completed within the required time frames. One investigation of post-approval studies of high-risk (class III) medical devices found that only 19% of FDA-required post-approval studies had been completed between three and five years post-approval.³⁶ Other evidence suggests that required post-market studies for drugs and biologics, similarly, are not completed in a timely manner.³⁷ Failure to conduct post-market studies means that medical products with outstanding issues regarding safety or

effectiveness at the time of approval are never fully evaluated, allowing for uncertainty with respect to these products' real-world safety and effectiveness.

Enforcement of post-market requirements is particularly important in the context of medical products granted conditional approval as part of an accelerated approval. A recent Government Accountability Office (GAO) study focused on drugs approved through expedited pathways found that the "FDA lacks reliable, readily accessible data on tracked safety issues and postmarket studies needed to meet certain postmarket safety reporting responsibilities and to conduct systematic oversight."³⁴ One example of delayed post-market enforcement in the accelerated approval context is ProAmantine (midodrine hydrochloride). The FDA originally approved midodrine in 1996 under accelerated approval for treatment of symptomatic orthostatic hypotension. The conditional approval required the submission of studies to prove that midodrine was effective for the approved use. The post-market studies were not completed as required. After the patent expired, and several generics had been approved for the U.S. market, finally, in 2010 (fourteen years after drug approval), the FDA began proceedings to withdraw the drug from the market.³⁸ Notably, this was the first withdrawal action of its kind.³⁹ The manufacturer then agreed to conduct the required studies by 2014, and was granted an extension until 2015.⁴⁰ The studies were then completed,⁴¹ and the first peer-reviewed article from the required post-market studies was published in 2016—twenty years after the drug was originally approved.⁴² This represents an unacceptably long period of uncertainty regarding the effectiveness of the drug for the approved use.

The FDA also needs more power to require that unsafe or ineffective drugs are taken off the market. With regard to food, medical devices and biologics, the FDA has mandatory recall power. This power is rarely used. However, with regard to drugs, the FDA currently lacks mandatory recall power, and can only request that a manufacturer

institute a recall of an unsafe drug. The FDA lacks the power to order a recall of an unsafe drug over manufacturer objection. A pending bill, H.R. 1108, the Recall Unsafe Drugs Act of 2017, would rectify this gap, and would provide provisions for emergency recall of a drug that presents an imminent threat of serious adverse health consequences or death. Finally, the FDA currently has the power to fine companies for lack of compliance with post-marketing requirements with civil monetary penalties of up to \$250,000 per violation,⁴³ can charge additional penalties if companies still do not comply with their statutory obligations, and as a last resort can deem a product misbranded. It is unclear that these enforcement mechanisms are sufficient, given the lack of timely completion of post-marketing studies for drugs, biologics and devices discussed above.

Recommendations

Congress should provide adequate funding and staffing for the FDA to monitor compliance with requirements for post-market studies, because these activities are not adequately supported by the Prescription Drug Users Fee Act.

The FDA should convene an expert panel to examine the use of fines and other existing penalties for failure to complete post marketing studies, to examine their effectiveness in compelling compliance by companies, and to suggest additional mechanisms to ensure timely completion of post-marketing requirements.

Congress should enact new legislation that requires manufacturers to enroll patient subgroups traditionally underrepresented in medical research, including the elderly, women, and racial and ethnic minorities, in similar proportions to disease prevalence, in post-market trials, to strengthen the generalizability of results, beyond the narrow patient populations in initial studies.

Congress should enact legislation that gives the FDA authority to order a drug recall, similar to its existing recall authority over food, medical devices and biologics.

3. Increase Access to Experimental Therapies Through Expanded Access Programs

Problem	Patients with serious and life threatening diseases should have access to experimental therapies under the FDA's authority to grant expanded access to these agents. Yet, even though the FDA approves the vast majority of requests for such access, companies often refuse to provide experimental therapies to patients.
Solution	Congress should enact legislation requiring study of the current barriers to expanded access to experimental treatments, and requiring reporting on recommendations for needed change.

While experimental drugs and biologics are in human clinical trials, only some people are eligible to participate in the trials. Each trial has inclusion and exclusion criteria that specify who is eligible to participate in the trial. How sick someone is, whether they have other health conditions, whether they can travel to the trial site, and other prescribed medications all effect eligibility.

The FDA has well-established expanded access mechanisms available for patients with serious or life-threatening conditions to obtain investigational drugs, biologics, and devices prior to approval, and outside of the clinical trial system, including in emergency situations.⁴⁴⁻⁴⁸ Manufacturers are permitted to charge patients for the manufacturing costs for the experimental agent.⁴⁷ A patient seeking expanded access must first obtain the approval of the manufacturer and only then, with a doctor's help, can apply to the FDA.

The FDA is often incorrectly blamed for companies' reluctance to provide expanded access to their experimental therapies. In the ten years between 2005 and

2014, the FDA approved 99.7% of patient applications for expanded access that had manufacturer approval.⁴⁹⁻⁵¹ Pharmaceutical companies often reject applications by patients with serious or life-threatening conditions for access to experimental drugs. An expanded access system that relies on the discretion of the companies developing new products is not “fair, just, thoughtful or efficient.”⁵² Companies' resistance to expanded access programs requires new policies that ensure access to experimental therapies for patients, but also address companies' concerns about cost-recovery, and the effects on approval timelines and evaluation by FDA.⁵³

A provision of the 21st Century Cures Act requiring pharmaceutical companies to publish information about their expanded access policies and procedures has just become effective. The law requires that manufacturers post information on their websites that includes contact information, procedures and criteria for requesting individual access, and the time frame for a decision on a request.⁵⁴ This is an important first step toward transparency in expanded access policies, but does not go far enough.

A bill recently introduced in the Senate, S. 1048, the Enhanced Clinical Trial Design Act of 2017, addresses some of the gaps in current law regarding access to experimental treatments. The bill includes provisions requiring the FDA to hold a public hearing regarding current mechanisms for access to experimental treatments, including: barriers to participation such as geographic and socioeconomic barriers, the effect of exclusion criteria on infants and children, pregnant and lactating women, the elderly, those with comorbid conditions or advanced disease; how to increase enrollment of diverse populations; and how changes in trial inclusion and exclusion criteria might affect trial length and complexity. Additional provisions require reports to Congress on whether existing law and regulations allowing expanded access need to be improved, and require recommendations for streamlining institutional review board review of requests to access experimental treatments.

Some ethicists have suggested that a national expanded access review board should be established to ensure that applications for expanded access are treated fairly, weighing the risks and benefits to the patient as well as the availability of the experimental agent.⁵² A transparent, independent organization could make these decisions, removing the perceptions of commercial influence over the decision process, and providing a more streamlined process for considering requests.

The discussion of access to experimental drugs prior to approval is complicated by recent efforts to enact state and federal "right to try" laws. These laws provide false hope to patients. Currently, 37 states have enacted such laws. These state laws are preempted by federal law, so they have had no actual effect. Not one patient has received an experimental therapy under any of these state laws.

The FDA must continue to have oversight over patient access to experimental therapies. Bills such as the Right to Try Act of 2017 (H.R.878), and the Trickett Wendler Right to Try Act of 2017 (S.204) have problematic provisions. First, they restrict the FDA's authority to prohibit dispensing and prescribing of experimental drugs, biologics and devices. Second, they prohibit the FDA from using evidence from the outcomes of experimental treatment dispensed in accordance with the bill in deciding whether or not to approve a medical product for the market. Finally, they defer to state definitions of "terminal illness," further reducing the FDA's role, and permitting uneven access to experimental treatment, determined by state of residency. If passed, these bills would allow patients to obtain unapproved drugs, biologics, and high-risk medical devices after only preliminary safety studies (Phase I studies) are completed, and before studies are done to further establish safety and to determine effectiveness. This would risk patients' health and safety by placing use of experimental medical products outside of rigorous scrutiny by health officials.⁵⁵ Moreover, passage of a federal right to try law would not address manufacturers' refusal to provide access to experimental products,

since there is no requirement that manufacturers provide experimental drugs or biologics.⁵⁶ Allowing manufacturers to charge for drugs provided under "right to try" could place patients at financial risk, since private and government-funded insurance programs typically do not cover experimental treatment. In addition, these federal bills also remove other important safeguards: they would immunize companies from any liability, even for grossly negligent behavior; and arguably permit companies to profit from the sale of experimental drugs.

Recommendations

Congress should enact legislation that requires study of the current barriers to expanded access to experimental treatments, and reporting on recommendations for needed change.

Congress should not enact legislation that circumvents the FDA's oversight over expanded access to experimental treatment, or that cedes authority over access to experimental treatment to the states.

4. Avoid Low Quality, Real-World Evidence

Problem	The use of real-world evidence, particularly low quality data, in pre-market approval decisions regarding new medical products, may compromise the approval process.
Solution	The FDA should continue to rely primarily on controlled, prospective, and randomized clinical trials in the pre-market evaluation process, and should incorporate high quality real world evidence in the post-market context.

Traditionally, clinical research takes place in highly controlled settings, where study sites and the participants are carefully selected according to strict criteria. The consequence is that many trials do not provide evidence that reflects the day-to-day realities of typical patient care. At the same time, large datasets containing rich patient data have become available. Examples include the FDA’s mini-Sentinel program and the federally funded Patient Centered Outcomes Research Institute’s (PCORI) PCORnet collaborative, both of which attempt to leverage routinely collected data from large health systems for post-market evaluation of medical product safety and effectiveness (although this work is predominantly focused on pharmacologic and biologic therapies). In response, there has been a movement toward the use of “real-world evidence”—that is, evidence derived from data gathered from actual patient experiences, in all their diversity. In many ways, this movement represents an important step toward a fundamentally better understanding of states of disease and health.

Broadly defined, the category of real world evidence includes not only rich, high quality data, but also low quality data, such as individual case reports, studies with

historical controls, single-arm trials (without a control group), non-representative patient surveys, and patient testimonials.

The 21st Century Cures Act requires the FDA to consider the use of real world evidence in applications to extend the use of already-approved drugs and biologics for new indications, to satisfy post-market study requirements for drugs and biologics, and in regulation of medical devices. Real world evidence is defined as “data regarding the usage, or the potential benefits or risks, of a drug derived from sources other than randomized clinical trials.”⁵⁷ The exclusion of randomized trial data from real world evidence in the law is concerning, because randomization is a key tool to restrict bias in research, and the two categories are not mutually exclusive.⁵⁸

We recommend that any use of real world evidence by the FDA be restricted to high quality data, and give preference to data from prospectively planned interventions, interventions that collect data on clinical endpoints, and pragmatic trials.⁵⁸

Use of real-world evidence for pre-market decision-making in medical product evaluation is inappropriate, subject to unmeasured confounding, and undermined by the fact that unapproved products are not in routine use in the real-world, prohibiting their study using ‘real-world’ data. Data from randomized, controlled, double blinded trials should remain the gold standard for approval.

In the post-market context, reliable, high-quality real-world evidence can be used to evaluate medical product safety and effectiveness from a more generalizable group of patients that better represents day-to-day realities of typical patient care.

Recommendations

The FDA should clearly and concretely define the term “real-world evidence” in all contexts to exclude data from single arm trials, trials using historical controls, non-representative patient surveys, case reports, and patient testimonials. The FDA should include data from prospectively planned interventions, interventions that collect data on clinical endpoints, and pragmatic trials in the definition of real world evidence.

Even though the 21st Century Cures Act excludes randomized studies from the category of “real-world evidence,” the FDA should make clear that prospective, randomized and controlled clinical trials cannot be replaced for pre-market evaluation with lower quality data. While real-world evidence may complement the information learned from these trials, it cannot reliably replace it.

5. Resist Efforts to Weaken Off-Label Marketing Restrictions

Problem	There has been recent industry pressure on the FDA to relax restrictions on the promotion of medical products for unapproved or “off-label” uses.
Solution	The FDA should not permit drug companies to market off-label uses of medical products, and the agency should continue to require adequate and well-controlled studies and approval for additional indications before marketing is permitted.

Since 1962, the FDA has required drug companies to demonstrate the safety and efficacy of each intended use for a drug and has prohibited companies from marketing unapproved, or “off-label” uses. This encourages drug companies to conduct rigorous clinical trials for new uses of drugs and to generate accurate data that can inform medical decisions, thereby protecting patients’ health.

This decades-old approach to evidence production has been threatened by a wave of litigation. Over the last few years, pharmaceutical companies have sought to take advantage of recent Supreme Court decisions that have expanded commercial speech rights. Relying on these decisions, the pharmaceutical industry has argued that off-label marketing is protected by the First Amendment, as long as it is not false or misleading. In 2012, the Second Circuit’s decision in *United States v. Caronia* raised First Amendment concerns with the way the government had prosecuted a pharmaceutical sales representative for making off-label claims.⁵⁹ In 2015, a district court in the Southern District of New York built on this ruling in *Amarin v. Food and Drug Administration*, and concluded that drug companies have a First Amendment right to market any off-label use to physicians, as long as the statements are “truthful and

nonmisleading.”⁶⁰ In the wake of these cases there has been immense pressure on the FDA to change the agency’s longstanding restrictions on off-label promotion.⁶¹⁻⁶³

Allowing drug companies to market unapproved uses of medicines invites companies to seek FDA approval for the narrowest clinical use and then market the drug broadly for any new use based on minimum evidence. While companies would need some evidence to support such marketing under the industry’s preferred approach, that evidence might be very weak, and far from what would be required to support a new indication. Preliminary indications that a drug is safe and effective for a particular use are often not validated in more robust trials.⁸ And drugs that are safe and effective for one indication can have very different results for another indication, making it imperative that data is produced and submitted to regulators for each new use. For example, Gabitril (tiagabine), approved to reduce the risk of seizures for those with epilepsy, was promoted off-label to patients without epilepsy.^{64,65} It turned out to have a paradoxical effect, sometimes causing seizures in those without epilepsy. Because tiagabine was approved for epilepsy, this risk was not initially recognized, and physicians sometimes increased the dosage after new-onset seizures.⁶⁶

Unfettered off-label marketing would disrupt the FDA’s ability to balance risks and benefits in approving a drug for specific indications. For example, in the case of opioids, there is a risk of addiction with each prescription. There is also a risk of death due to respiratory depression at high doses. Some strong opioids, like OxyContin (oxycodone), are approved only for moderate to severe pain for those needing round-the-clock pain relief on an ongoing basis. OxyContin is not approved for as-needed pain relief, or for mild pain. The FDA considered the risks, for those with severe ongoing pain, to be outweighed by the pain relief benefit. The *Amarin* decision would permit companies to market OxyContin for mild pain, as long as they made only true

statements.⁶⁷ Advertising OxyContin as effective for mild pain would be truthful, but could put patients at risks deemed not worth the benefits for this indication by the FDA.

Allowing advertisement or marketing of drugs based upon limited results from preliminary trials may also result in the use of medications that are ineffective or unproven for a condition in place of existing, proven treatments.⁶⁷ A recent study found that 80% of off-label prescriptions lacked strong evidence to support their use, and that patients who received drugs prescribed for off-label use that lacked strong evidence were 54% more likely to experience an adverse drug event than those who received a drug for an approved use.⁶⁸

Off-label marketing can be extremely effective in changing prescribing patterns, despite a lack of evidence supporting off-label uses. For example, Pfizer's promotion tactics for Neurontin (gabapentin) were so aggressive that during the drug's first decade on the market, 83 percent of prescriptions were for off-label uses.^{69,70} Yet the majority of these off-label uses had little evidence to support them, and provided less optimal treatment than other medications already approved for those uses.⁷¹ Ultimately, the Department of Justice (DOJ) pursued criminal charges against Pfizer for its off-label marketing, and Pfizer pled guilty to two felonies and paid \$430 million in fines.⁷²

A retreat from the FDA's historical prohibition on off-label marketing would distort the evidence base for medicines, expose patients to greater risks, and increase pharmaceutical spending for uses of medicines that have not been proven to be effective and safe. Fortunately, the recent First Amendment cases do not require the FDA to take such a step. *Amarin*, as a mere district court opinion, is not binding on other courts. The *Caronia* case binds courts in several states (but not nationally), and left open key arguments that the FDA can make to defend its approach in future prosecutions, even in the Second Circuit. (Courts as a rule only address the arguments before them. It is therefore possible to prevail on a different theory in a later case even after losing with

prior arguments.) For instance, the case did not directly determine that the FDA could not treat off-label marketing as evidence of a crime, rather than a crime itself—a justification that has long-protected the FDA’s approach to off-label marketing in other jurisdictions.⁷³ In addition, even if the FDA’s approach is understood directly to regulate commercial speech, under the governing *Central Hudson* test, commercial speech may be regulated to ensure that the public is adequately informed. Properly understood, the FDA’s historical approach serves this end, because it is well-tailored to a substantial need: the production of high quality evidence, that can then be reviewed by expert regulators.

We are heartened by the FDA’s recent draft guidance documents and memorandum indicating its proposed position on off-label promotion.⁷⁴⁻⁷⁶ The FDA and the U.S. Department of Justice (DOJ) should aggressively defend the FDA’s ability to restrict off-label promotion. The DOJ, in collaboration with federal health agencies, should defend off-label marketing restrictions as essential to the creation of more speech—evidence needed to evaluate the efficacy and safety of drugs—and should continue to prosecute off-label promotion under the False Claims Act as appropriate.

Recommendations

The FDA should not revise its current rules or guidelines to permit drug companies to engage in more communications about off-label uses than are currently permitted. The draft FDA guidance documents released in early 2017 should be adopted as final guidance documents.

The FDA and DOJ should continue to prosecute cases of off-label promotion, and commit to fully litigating the First Amendment issue.

The FDA and DOJ should be transparent regarding their approach in enforcing restrictions on off-label marketing, including how they litigate off-label cases, settle them, and negotiate with pharmaceutical companies.

6. Strengthen Regulation of Medical Devices

Problem	Both pre-market and post-market evaluation and surveillance for medical devices are weaker than they are for drugs and biologics.
Solution	The FDA should increase the regulatory standards for moderate-risk and high-risk devices. Moderate-risk devices should be more rigorously evaluated prior to market clearance. New high-risk devices requiring pre-market approval should be approved only based upon evidence from randomized, controlled trials.

The approval process for medical devices differs from that used for drugs and biologics. Medical device regulatory approval is based on the device's underlying risk. Class I (lowest-risk) devices, like tongue depressors, do not require pre-market approval. This is appropriate.

Class II (moderate-risk) devices require pre-market notification to the FDA, and are cleared for the market based on a manufacturer's certification that the device is substantially equivalent to a previously marketed device, called a 510(k) submission. While some manufacturers must submit clinical data as part of pre-market review of Class II devices, clinical data is not routinely required for clearance or post-market surveillance. We support the Institute of Medicine's 2011 recommendations that the 510(k) submission process for Class II devices be replaced with a regulatory framework that more rationally evaluates safety and effectiveness of devices in both the pre-market and post-market context.⁷⁷ This will require new legislation.

Class III devices (highest-risk), require pre-market approval by the FDA on the basis of clinical studies, and frequently require post-market study commitments. The FDA should strengthen its current regulatory requirements for clinical trial data in the

context of evaluating pre-market applications for Class III devices. Recent research suggests that these requirements lead to, on average, one feasibility trial of 50 patients and one pivotal trial of 250 patients being conducted to provide evidence of safety and effectiveness for these highest-risk devices with only half being randomized, controlled trials.³⁶ These regulatory requirements should be maintained in applications for expanded indications for use in already approved Class III devices through PMA Supplements.

Class III devices should be approved based upon randomized, controlled trials using clinical outcomes for trial endpoints, with blinding as appropriate, and an adequate follow-up. We oppose Class III medical device approvals based on observational data and trials without a control group as these do not provide sufficient evidence to demonstrate safety and effectiveness. When Class III devices have been cleared for marketing based upon the less stringent 510(k) criteria, patients have been exposed to unnecessary risks, and recalls have been issued as a result.⁷⁷⁻⁸⁰ In the past, lower evidentiary requirements have resulted in premature device approval, with subsequent high quality evidence demonstrating that the approved devices had no benefit.⁸¹

To enhance post-market evaluation, the FDA should enforce the requirement, currently being phased in on a schedule, that all medical devices are labeled with a unique device identifier, including Class I, II, and III devices, by 2020.⁸² In addition, the FDA should advocate that electronic health record vendors, and health plans, including federal payers, modify their medical record and administrative claims forms to include the unique device identifier as part of routine patient care billing, to enable post-market evaluation of medical device safety and effectiveness using routinely collected data.

Recommendations

The FDA should convene an expert panel to recommend legislative changes to provide an updated framework for regulation of Class II devices that accounts for safety and effectiveness across the device lifecycle, as recommended by the Institute of Medicine.

The FDA should strengthen its current regulatory requirements for clinical trial data for evaluating pre-market applications for Class III devices. In addition, FDA should evaluate industry compliance with post-marketing requirements, including the establishment of tracking systems, reporting of device malfunctions, serious injuries or deaths, post-market surveillance studies as well as post-approval studies required at the time of approval of a pre-market approval (PMA).

The FDA should enforce the requirement that all medical devices are labeled with a unique device identifier and that all health plans and federal payers, including the Centers for Medicare and Medicaid Services, modify their standard administrative claims billing file to include a data element for the unique device identifier.

7. Improve Access to Clinical Trial Data, Including Patient Level Data, Summary Level Data and Meta-Data

Problem	Lack of access by independent researchers to de-identified patient level data, summary level data and meta-data from clinical trials can obscure serious safety and efficacy problems with new and existing medical products. Lack of information about the basis for FDA regulatory actions and decision-making can harm medical decision-making.
Solution	The FDA should provide researchers access to de-identified clinical trial data submitted by drug and device manufacturers to support regulatory approval and post-marketing requirements. The FDA should enforce clinical trial registration and reporting requirements, and impose penalties for noncompliance. The FDA should adopt the recommendations of the FDA Transparency Working Group which will provide increased transparency of FDA regulatory actions and decision-making.

Open access to clinical data for use by independent researchers is important because some drugs are approved, and only later determined, based on secondary analyses, to be less effective or to cause serious side-effects that were not known at the time of approval. For example, after Vioxx (rofecoxib) was withdrawn because of increased cardiovascular risk, using data made available during litigation, independent researchers, who had served as expert witnesses in litigation, conducted a cumulative pooled analysis of all known placebo-controlled studies of the drug. Their evaluation showed that the increased cardiovascular risk became more apparent over time, as more studies were completed by the manufacturer, although these studies were not consistently published, nor were safety results made available to the scientific community.⁸³ While these data were uniquely made available via the litigation, enabling

this research study, most medical product litigation settlements and final orders do not allow for external access to the clinical research data supporting the efficacy and safety of the product involved.

The lack of benefit from approved therapies can also be demonstrated by independent research. A meta-analysis of reported trials and complete clinical study reports for Tamiflu (oseltamavir) showed that despite government stockpiling of the drug for influenza, it provided little benefit, yet exposed patients to toxicity.⁸⁴ The Institute of Medicine has identified the importance of reanalysis by independent researchers, citing research identifying increased risks of suicidality for adolescents prescribed selective serotonin reuptake inhibitors, research evaluating the risk of heart attack for patients prescribed Avandia (rosiglitazone), and the selective outcomes reporting for off-label use trials for Neurontin (gabapentin).⁸⁵

Independent researchers are often able to identify safety signals in the original data that the original reviewers missed.^{86,87} Access to the full universe of data will ensure that independent researchers can scrutinize the existing data for accuracy, conduct meta-analytical studies and follow-up studies to validate the result of previous studies, and provide a more comprehensive understanding of the possible risks and benefits of a particular drug or device to inform doctors, patients, and public and private payers. Data can be safely released to independent researchers once it is de-identified to protect patient privacy. There are recognized industry standards for de-identification that ensure that a secondary researcher cannot identify a clinical trial participant from the data.^{85,88}

Yet a large proportion of trial results are never reported, either on the federal trials registration website, [ClinicalTrials.gov](https://clinicaltrials.gov), or in peer-reviewed journals. The failure to disseminate research findings and to share data with independent researchers has significant negative health and healthcare consequences. Incomplete data about the

safety and efficacy of medical products means that health care providers are making clinical decisions about the care of their patients with limited information, and that public payers and private insurers are making decisions about coverage and reimbursement for these products with only partial information. Under authority granted by the Food and Drug Administration Amendments Act of 2007, the FDA is charged with enforcement of the requirement that researchers register trials and report results on ClinicalTrials.gov. However, for the majority of clinical trials completed between 2008 and 2012, and subject to these registration and reporting requirements, trial results were not reported on ClinicalTrials.gov.⁸⁹

Under the terms of international agreements, pharmaceutical companies typically submit similar approval information to drug regulatory agencies worldwide. The European Medicines Agency is prospectively requiring release of summary-level data and meta-data, and will soon release de-identified patient-level data to the public. Health Canada has also proposed the enactment of new regulations to allow prospective release of clinical summaries, reports and supporting data of completed clinical trials. Currently, the FDA provides the action package for approval for new drugs and biologics on their website, which contains detailed scientific and statistical analyses prepared by agency staff. However, additional information is only available if a researcher files a Freedom of Information Act request and is successful. We support existing laws requiring the registration of clinical trials, along with results reporting, and also believe that as a matter of course the FDA and researchers should prospectively release information on at least as generous terms as released by the European Medicines Agency.

The FDA launched a Transparency Initiative in 2009, which recommended better agency communication to the public and industry, by creating simple to understand guides for the public, by releasing more information on its website about medical

products and regulation, and by releasing information about agency decision-making. The FDA implemented many, but not all of the proposals recommended by the Transparency Task Force. For example, one proposal that has not been implemented is a proposal to share pooled de-identified patient-level data used by the FDA to analyze risks and benefits across trials and manufacturers.

A recent report by the FDA Transparency Working Group, a group of independent researchers, provides a comprehensive blueprint for transparency changes that will advance the development of safe and effective medical products.^{90,91} We fully endorse these recommendations, which include recommendations for the FDA to disclose: more information about key milestones in the application process; more of its own analysis and decision making; more about the application and review process for generic drugs and follow-on biologics; information correcting misleading information in the market; and data from scientific studies to enhance understanding of medical products.^{90,91}

Recommendations

Congress should enact legislation requiring disclosure to public health, clinical, and basic science researchers of all clinical trial data provided to the FDA as a condition of approval. Data disclosed should include summary-level data, meta-data, and de-identified patient-level data including case reports.

The DOJ should implement a policy requiring sharing of legacy and future clinical trial data by pharmaceutical companies, including summary-level data, meta-data, and de-identified patient-level data, as a condition of settlement in cases brought against pharmaceutical companies.

The FDA should enforce existing reporting requirements for registering and reporting results for completed clinical trials through the National Institute of Health's public clinical trial registry, [ClinicalTrials.gov](https://clinicaltrials.gov).

Congress should enact legislation requiring that clinical trial data from post-market studies provided to the FDA, including summary-level data, meta-data and de-identified patient-level data, be made available in an easily accessible manner to researchers.

The FDA should adopt all of the recommendations of the FDA Transparency Working Group.

Conclusion

Ensuring the safety and efficacy of medical products used by millions of Americans is a sacred duty of the FDA. The efficient and timely approval of new drugs, devices and biologics need not be in conflict with the need for generating high-quality, rigorous evidence about these products before they reach the market. In this policy paper, we offer recommendations that reconcile these two important functions of the FDA. However, strengthening the agency requires pro-active measures by the Trump Administration, the FDA and its commissioner Dr. Scott Gottlieb and the US Congress. A collective renewal of our commitment to the FDA's mandate and an investment in resources for the agency will ensure that patients' health is safeguarded, while the expenditures on drugs, biologics and devices are being devoted to products that are actually beneficial in the long-run.

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