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SYMPOSIUM

Blueprint for Transparency at the U.S. Food and Drug Administration

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LETTER FROM THE EDITOR

The *Journal of Law, Medicine & Ethics* always strives to be at the forefront of research and policy making. We aim to publish articles that reexamine and expand on the current literature and that create a path forward in medicine, law, ethics, and the many other sub-fields in health and health law. We hope every article we publish contributes to the voluminous literature in a positive way and that our readers are invigorated by the spirited discussion. This supplement issue of *JLME* continues this multi-disciplinary approach with “Blueprint for Transparency at the U.S. Food and Drug Administration.” Here guest editors Anna L. Davis, James Dabney Miller, Joshua M. Sharfstein, and Aaron S. Kesselheim and their co-authors have tackled the challenging topic of transparency at the respected government agency. A team of researchers from various universities wrote the main “Blueprint” article of this supplement issue, which is followed by six commentary articles. The Blueprint article recommends 18 specific ways the FDA can be more transparent so that the public at large can be better informed about medical products, applications, and scientific studies. The commentary articles then discuss what may work, the missed opportunities and limitations of the suggestions, and legal approaches and guidelines for the FDA to take. Ultimately, the hope is that the FDA will disclose more throughout its review process, and do so without disrupting trade secrecy protections, in order to improve the public’s health.

In the spirit of disclosure, I offer my own. After ten years as the assistant editor of *JLME*, I am creating my own path forward and focusing on a new chapter in my life. Working for our parent organization ASLME and editing this journal have been a tremendous professional and personal honor. To our readers, authors, and peer reviewers: thank you for the many years of stimulating conversations and teaching opportunities. To my friends at ASLME: thank you for being the best group of co-workers anyone could ask for. To my editor and mentor Ted Hutchinson: a huge thank you for always believing in me and for your continued support.

Thank you for a great run! I look forward to staying in touch with you.

With best wishes,
Courtney

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THE JOURNAL OF
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Symposium Articles

SYMPOSIUM

**Blueprint for
Transparency at the
U.S. Food and Drug
Administration**

Guest edited by
Anna L. Davis,
James Dabney Miller,
Joshua M. Sharfstein,
and
Aaron S. Kesselheim

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*Letter from
the Editor*

Cover image ©Getty

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INTRODUCTION

*Anna L. Davis, James Dabney Miller,
Joshua M. Sharfstein, and Aaron S.
Kesselheim*

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**Blueprint for Transparency at the
U.S. Food and Drug Administration:
Recommendations to Advance the
Development of Safe and Effective
Medical Products**

*Joshua M. Sharfstein, James Dabney
Miller, Anna L. Davis, Joseph S. Ross,
Margaret E. McCarthy, Brian Smith,
Anam Chaudhry, G. Caleb Alexander,
and Aaron S. Kesselheim*

BACKGROUND

The U.S. Food and Drug Administration (FDA) traditionally has kept confidential significant amounts of information relevant to the approval or non-approval of specific drugs, devices, and biologics and about the regulatory status of such medical products in FDA's pipeline.

OBJECTIVE

To develop practical recommendations for FDA to improve its transparency to the public that FDA could implement by rulemaking or other regulatory processes without further congressional authorization. These recommendations would build on the work of FDA's Transparency Task Force in 2010.

METHODS

In 2016-2017, we convened a team of academic faculty from Harvard Medical School, Brigham and Women's Hospital, Yale Medical School, Yale Law School, and Johns Hopkins Bloomberg School of Public Health to develop recommendations through an iterative process of reviewing FDA's practices, considering the legal and policy constraints on FDA in expanding transparency, and obtaining insights from independent observers of FDA.

RESULTS

The team developed 18 specific recommendations for improving FDA's transparency to the public. FDA could adopt all these recommendations without further congressional action.

FUNDING

The development of the *Blueprint for Transparency at the U.S. Food and Drug Administration* was funded by the Laura and John Arnold Foundation.

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**Transparency at the U.S. Food and
Drug Administration**

Robert M. Califf

Given the profound public health and economic ramifications of decisions made by the U.S. Food and Drug Administration, the degree to which FDA activities should reflect an approach founded on complete transparency versus one focused on preserving confidentiality of information deserves public discussion. On one hand, reasonable requirements for transparency are critical to stimulating effective innovation, knowledge dissemination, and good business practice. On the other, ensuring the vitality of the medical products industry requires protecting legitimately proprietary information. With current standards reflecting a lengthy accumulation of legal, regulatory, and practical precedent, recent significant changes in the environment in which the FDA operates should prompt a critical examination of current practices. In this article, I comment on Sharfstein and colleagues' "Blueprint for Transparency," which calls for multiple specific actions to increase transparency at the agency across five key areas, including interactions between FDA and industry, public disclosure of internal FDA analyses, deliberations concerning generics and biosimilars, expanded access to raw study data, and approaches to countering misleading information in the public sphere. I evaluate these recommendations in light of my experience as a clinician, researcher, and former FDA Commissioner, and reflect on possible outcomes that could result from enacting these practices.

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**FDA Transparency in an Inescapably
Political World**

Daniel Carpenter

Transparency requires more than disclosure of data. It requires a mechanism and policy for conveying information to the public. In order for the aims of the excellent report of the FDA Transparency Working Group to be realized, a publicity initiative will need to accompany the plan of action. The FDA will need to actively convey information about the evidence concerning benefit-risk profiles of drugs, sometimes pointing out misleading claims by manufacturers or sponsors. In other cases, the FDA will need to make available its procedures, including possible conflicts of interest, not only in drug approval, but also in guidance documents and in rulemaking. Transparency as a process of letting the public see into the agency should be accompanied by a proactive strategy of distributing information about the products regulated by the agency.

Symposium articles are solicited by the guest editor for the purposes of creating a comprehensive and definitive collection of articles on a topic relevant to the study of law, medicine and ethics. Each article is peer reviewed.

Independent articles are essays unrelated to the symposium topic, and can cover a wide variety of subjects within the larger medical and legal ethics fields. These articles are peer reviewed.

Columns are written or edited by leaders in their fields and appear in each issue of *JLME*.

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The Transformation of Informed Consent

A Symposium Guest Edited by Susan M. Wolf, Ellen Clayton, and Frances Lawrenz

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Clinical Trial Transparency: The FDA Should and Can Do More**

Amy Kapczynski and Jeanie Kim

The *Blueprint for Transparency at the FDA* recommends that the FDA proactively release more clinical trial data. We show that the FDA possesses the legal authority to act on this recommendation, and describe several reasons that the agency should do so. In particular, the primary existing route for researchers to obtain access to this data, the Freedom of Information Act (FOIA), has important limits, as our own recent experience shows.

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FDA and the Marketplace of Ideas for Medical Products**

Nathan Cortez

The market can produce skewed information about investigational products awaiting FDA approval. But the FDA rarely steps in to correct such misleading information, despite statutory authority to do so. This article evaluates a recommendation by the FDA Transparency Working Group that FDA more clearly signal when and how it will correct misleading information about investigational products, and why such a recommendation is particularly important after the 21st Century Cures Act.

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Disclose Data Publicly, without Restriction**

Peter Doshi and Tom Jefferson

Ethical, evidence-informed decision making is undermined by the grave concerns that have emerged over the trustworthiness of clinical trials published in biomedical journals. The inescapable conclusion from this growing body of research is that what we see, even in the most highly regarded peer-reviewed journals, cannot be trusted at face value. Concerns of inaccurate, biased, and insufficient reporting of trials are impossible to resolve without access to underlying trial data. Access to such data, including things like clinical study reports—huge, unabridged, detailed reports of clinical trials—would minimize the risk of distortions and selective publication. But the FDA, the world's greatest custodian of those data, just sits on them. We see no reason why FDA should not publicly release clinical study reports with minimal redactions. The European regulator is already doing this, but FDA's holdings are far greater. Data transparency is not simply an "opportunity" FDA might consider, but rather an ethical imperative. The *Blueprint* is good but does not go far enough. We do not need gates, barriers and committees between us and access to aggregate reports on drugs and other interventions which we are prescribing or using daily. Let's leave the nannies at home.

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Withholding Information on Unapproved Drug Marketing Applications: The Public Has a Right to Know**

Sammy Almashat and Michael Carome

The Food and Drug Administration (FDA), as a matter of long-standing policy, does not inform the public of instances whereby applications for new drugs or new indications for existing drugs have been rejected by the agency or withdrawn from consideration, nor does it disclose the agency's analyses of the data submitted with such applications. This lack of transparency is unjustified and prevents patients, researchers, and healthcare providers from gaining insight into why a drug's application was not approved. The FDA's policy is particularly troubling in cases where the agency has found a currently marketed drug to be ineffective or unsafe for a newly proposed indication. Disclosure of the FDA's findings in such cases would promote public health by encouraging healthcare providers to avoid prescribing drugs for unapproved (off-label) uses that the agency has deemed to be potentially dangerous or ineffective. The FDA's counterpart agencies in Europe and Canada have demonstrated the feasibility of disclosing information on rejected and withdrawn drug marketing applications. The FDA should follow suit and allow the American public to know when a drug is deemed unsafe or ineffective for a certain use.

INTRODUCTION

*Anna L. Davis, James Dabney Miller, Joshua M. Sharfstein,
and Aaron S. Kesselheim*

Patients are angry that a once-promising drug in development has disappeared without a trace. Companies wait before developing a generic drug because they do not know how many others are in the pipeline. Physicians express frustration at company statements misrepresenting the data about a medication. In each of these scenarios, key information that could resolve the issue may have been transmitted to the U.S. Food and Drug Administration (FDA), but manufacturers' efforts to maintain confidentiality protections and the FDA's current disclosure rules supporting those claims keep the information from the public eye. Can the FDA take better approaches to transparency that can simultaneously support the public health and not undermine appropriate recognition of trade secrets?

This issue of the *Journal of Law, Medicine & Ethics* is devoted to the *Blueprint for Transparency at the U.S. Food and Drug Administration*. Developed by a team of researchers from Harvard Medical School/Brigham and Women's Hospital, Yale, and Johns Hopkins, and supported by funding from the Laura

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& John Arnold Foundation, the Blueprint sets forward 18 specific recommendations for agency action on transparency. These ideas support greater disclosure about product applications, failed and withdrawn products, and scientific studies. To encourage discussion on these ideas, the editors invited commentaries from a range of experts in medicine, law, public policy, and regulatory science.

The first commentary is by Robert Califf, who was FDA Commissioner from February 2016 to January 2017. In his commentary, among other points, Dr. Califf tempers his support for greater transparency with caution about some of the difficulties in implementing several of the recommendations. He concludes with "unabashed enthusiasm" about FDA correcting misinformation in the marketplace and calling for FDA to provide more rapid guidance on its thinking about key scientific topics.

The second commentary is by Daniel Carpenter from the Government Department at Harvard University. Professor Carpenter argues that the Blueprint should have tackled transparency issues related to the influence of regulated industry — including disclosure of all potential avenues of this influence in the guidance and rulemaking process. He also notes that countering misleading information in the market, while important, is a fraught and politicized task.

The third commentary is by Amy Kapczynski and Jeanie Kim from Yale Law School. They discuss the practical limitations of the Freedom of Information Act as a route to obtain information from FDA. They also provide an analysis of FDA's legal authority to disclose information proactively.

The fourth commentary is by Nathan Cortez from the Dedman School of Law of Southern Methodist University. He calls on FDA to lose its traditional reti-

cence to question industry disclosures under securities laws, by establishing guidelines for identifying and correcting misleading information.

The fifth commentary is by Peter Doshi at the University of Maryland School of Pharmacy and Tom Jefferson at the Centre for Evidence Based Medicine of the University of Oxford. They discuss publication and other biases that, in their view, would be ameliorated by release of certain types of clinical trial data by FDA. They do not support the Blueprint's idea of having an independent organization or group review proposals for scientific merit before releasing data.

The final commentary is by Michael Carome and Sammy Almashat at Public Citizen. They emphasize the benefits of disclosing information about product applications that are not approved, or are withdrawn or abandoned. These include more rapid abandonment of unfruitful lines of research and clinical prac-

tice, to the benefit of patients, as well as the more efficient pursuit of more fruitful avenues of exploration, also to the benefit of patients.

What emerges from this collection of perspectives is a clear sense that transparency supports the FDA's mission as a public health agency and that it should be seen as the norm, with exceptions carved out to account for trade secrecy protections, rather than the other way around. There is general recognition that a strong foundation in transparency can contribute to enhanced patient outcomes, efficient market dynamics, and a greater public trust in the extremely important work of the FDA.

Note

The authors have no conflict of interest to declare.

Blueprint for Transparency at the U.S. Food and Drug Administration: Recommendations to Advance the Development of Safe and Effective Medical Products

Joshua M. Sharfstein, James Dabney Miller, Anna L. Davis, Joseph S. Ross, Margaret E. McCarthy, Brian Smith, Anam Chaudhry, G. Caleb Alexander, and Aaron S. Kesselheim

Overview and Scope

The U.S. Food & Drug Administration (FDA) stands apart among the world's regulatory agencies for the depth of its expertise and analysis about medical products. However, much of this knowledge and information about the regulatory process stay within FDA's walls, as a result of policies and regulations that have for many years broadly defined what is considered "confidential."

In 2010, FDA established a Transparency Task Force to consider whether these regulations and policies should be modernized.¹ The Task Force quoted former Commissioner Donald Kennedy in saying that "government decisions, particularly regulatory decisions, should be based on publicly available information...people affected by government decisions have a right to know the basis on which they are made." The Task Force released a series of draft recommendations, several of which were adopted.²

Since 2010, the ground has tilted further in favor of transparency at the FDA. Patient advocates, academic researchers, and legislators have expressed frustration

about policies that prevent understanding of the pipeline for new drugs. In place of the FDA, third parties are aggregating disclosures by medical product companies to investors and selling them as information services. In certain high profile cases, companies have released misinformation that FDA was unable to counter in a timely way. Litigation is also putting pressure on the Agency to change its policies on confidentiality.³

The world around the Agency has also become more transparent. Extensive information on most clinical trials is publicly available on the website www.ClinicalTrials.gov, hosted by the National Library of Medicine of the National Institutes of Health. The European Medicines Agency is advancing a broad transparency initiative that includes the release of many their analyses as well as certain industry submissions.

The potential benefits of greater transparency in the regulatory process include:

- A higher quality and greater quantity of evidence to inform medical education and guide clinical practice;

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- Faster innovation, as researchers, industry, and investors can more easily and thoroughly understand successes and failures;
- Improvements in FDA processes, allowing researchers to study how companies and FDA interact; and
- Greater public understanding and confidence in the activities of the FDA.

A change in the presidential administration is an opportune time to take a fresh look at FDA’s policies and practices to support public transparency. With support from the Laura and John Arnold Foundation, a team of academic faculty — at the Johns Hopkins Bloomberg School of Public Health, Brigham and Women’s Hospital and Harvard Medical School, Yale Medical School, and Yale Law School — has developed a Blueprint for Transparency at FDA.⁴

This iterative process included reviewing the work of the 2010 Transparency Task Force, understanding recent activities by the European Medicines Agency, evaluating published research on the FDA review process, obtaining insight from close Agency observers with a variety of perspectives (including patient advocacy organizations, pharmaceutical companies, consumer organizations, and other academic experts), and considering a range of constraints on what might be possible. This work recognizes the importance of legal restrictions on disclosure of trade secrets, for which federal law requires confidentiality.⁵

The report has five focus areas:

1. FDA should disclose more information about key milestones in the application process.
2. FDA should disclose more of its own analysis and decision-making.
3. FDA should disclose more about the application and review process for generic drugs and biosimilars.
4. FDA should correct misleading information in the market.
5. FDA should disclose data from scientific studies to enhance understanding of medical products.

Together, these sections contain 18 recommendations, which are summarized in the Table.⁶

Progress on transparency at FDA does not require an Act of Congress. Under existing statutory authority, FDA has broad discretion to define much of what is considered confidential by amending its regulations and refining policy.⁷ The recommendations in this Blueprint represent realistic steps FDA can take without statutory change to provide the public substantially more information on regulated medical products, and in doing so, improve patient care and product development — advancing the public’s health.

Table

Blueprint for Transparency at FDA: 5 Focus Areas with 18 Specific Recommendations

Focus Areas	2010 FDA Transparency Task Force	New Recommendations
<p>FDA should disclose more information about key milestones in the application process.</p>	<ul style="list-style-type: none"> • FDA should disclose basic information (including name of sponsor and product) about investigational notices, the filing of marketing applications, and the existence of clinical holds. (1) 	<ul style="list-style-type: none"> • FDA should include in disclosures of investigational notices and marketing applications the class of medication and mechanism of action if known. (2) • FDA should include in disclosures of investigational notices and new applications the ClinicalTrials.gov numbers for all trials conducted or relied upon as pivotal for marketing approval. (3) • Where FDA enters into a Special Protocol Assessment, FDA should release the text relevant to safety and efficacy after the study is completed. (4) • When FDA has issued or released a clinical hold related to safety or efficacy, the FDA should release a summary of the reasons within 10 days. (5) • FDA should disclose whether a marketing application has been designated for an expedited development or review program and, if so, provide the scientific basis for that designation. (6) • FDA should disclose written requests for pediatric studies at the time such requests are made, as well as other documents indicating agreement on changes to the initial request. (7)

Table (continued)

Blueprint for Transparency at FDA: 5 Focus Areas with 18 Specific Recommendations

Focus Areas	2010 FDA Transparency Task Force	New Recommendations
FDA should disclose more of its own analysis and decision-making.	<ul style="list-style-type: none"> FDA should provide information and explanations for withdrawn medications and should disclose FDA's communications to companies when products are not approved. (8) 	<ul style="list-style-type: none"> FDA should make public its clinical and statistical reviews of products not approved or for which the marketing applications are abandoned or withdrawn. FDA should issue guidance on the definition of abandonment. (9) FDA should make its pooled data sets, masked and de-identified as appropriate, and FDA's analyses of these data sets, available to the medical and research community through clinical data repositories, such as through the National Institutes of Health Biologic Specimen and Data Repository Information Coordinating Center. (10)
FDA should disclose more about the application and review process for generic drugs and follow-on biologics.	<ul style="list-style-type: none"> FDA should disclose the filing of generic drug applications, including the name of the sponsor and the name of the reference drug to be copied. (11) 	<ul style="list-style-type: none"> FDA should routinely disclose those portions of Complete Response Letters to generic drug manufacturers that relate to bioequivalence. (12) FDA should routinely disclose the filing of abbreviated biologics licensing applications, including the name of the sponsor, the reference biologic product, and whether the application is for "biosimilarity" or "interchangeability." (13) FDA should routinely disclose those portions of a Complete Response Letter with respect to an abbreviated biologics licensing application that relate to the biosimilarity to or interchangeability with the reference biologic product. (14)
FDA should correct misleading information in the market.		<ul style="list-style-type: none"> FDA should correct misleading information where there is the potential for substantial confusion about the safety or efficacy of the medical product for both approved and unapproved uses (15)
FDA should disclose data from scientific studies to enhance understanding of medical products.		<ul style="list-style-type: none"> FDA should disclose Clinical Study Reports that have been submitted to FDA in support of a marketing application. To the extent possible, FDA should harmonize standards on CSR release with the European Medicines Agency. (16) FDA should release the final reports that fulfill Postmarketing Requirements and Postmarketing Commitments, including Clinical Study Reports of Phase IV Studies and other post-approval reports, at the time FDA considers the sponsor's obligation to conduct a study to be fulfilled. (17) When there are clinical trial data, including patient-level data, that are not available to independent investigators through industry-sponsored websites, then FDA should make data available through clinical data repositories, such as through the National Institutes of Health Biologic Specimen and Data Repository Information Coordinating Center, with policies on deidentification to protect patient privacy. (18)

FDA Should Disclose More Information about Key Milestones in the Application Process

Background

Under the Food, Drug, & Cosmetic Act, the sponsors of new drugs, biologic products, and many medical devices seek approval or clearance from FDA prior to marketing.⁸ The FDA review process includes several key steps that provide opportunities for transparency.

The first major milestone in the regulatory process occurs when sponsors submit notice to FDA about plans to conduct clinical studies. For drugs and biologics, this notice is called the Investigational New Drug application (IND). For medical devices, it is the Investigational Device Exemptions application (IDE). FDA regulations set out the requirements governing the format and content of these notices.

Sponsors may proceed with clinical studies 30 days after filing an investigational application unless FDA disapproves an Investigational Device Exemptions application or notifies the sponsor that the investigation may not begin, or, in the case of an Investigational New Drug application, issues a “clinical hold.”⁹ A clinical hold means that the clinical trial in question may not go forward as a result of concerns over the health and safety of participants.¹⁰ FDA can impose a clinical hold on a study at any time during its progress and may lift a clinical hold once concerns are addressed.

During a drug’s clinical trial period, the sponsor and FDA may negotiate a Special Protocol Assessment (SPA), a written agreement covering the design of clinical trials in support of a marketing application.¹¹ The Special Protocol Assessment is binding on FDA, meaning that FDA accepts that if trials with the characteristics enumerated in the Special Protocol Assessment are successful, then they will fulfill an important requirement for approval. Nonetheless, FDA may alter or void a Special Protocol Assessment if a “substantial scientific issue” is identified after the trial begins.

Filing of the Application

After clinical data are collected, the next key step is the filing by the sponsor of a marketing application with FDA. For new drugs, sponsors are required to file a New Drug Application (NDA); for biologic products, sponsors must file a Biologics License Application (BLA).¹²

FDA oversight of medical devices varies according to a device’s risk to patients. Many low-risk medical devices, such as tongue depressors, do not require premarket notification submission to FDA to be legally marketed. By contrast, the sponsor of a moderate- or high-risk medical device usually files either a 510(k)

premarket notification or a Pre-Market Approval application (PMA).¹³

Expedited Review Programs

Congress has approved numerous programs intended to expedite the clinical development and regulatory review of applications for drugs and biologics of particular clinical importance. Some of these include the Fast Track, Breakthrough Therapy, Accelerated Approval, and Priority Review pathways. These programs have different and complex requirements but are often referred to collectively as “Expedited Programs.”¹⁴ Sponsors of new drugs that FDA designates as potential treatments for rare diseases (‘orphan drugs’) also receive an array of benefits intended to encourage the development of treatments for these diseases.¹⁵ Most recently, Congress, in the 21st Century Cures Act, provided for expedited development of regenerative advanced therapies.¹⁶

Devices can also qualify for a priority review. A pilot program started in 2015 offered the prospect of increased regulatory attention and hence expedited development for devices that reflect “breakthrough technologies” for life-threatening or irreversibly debilitating diseases or conditions.¹⁷ This pilot program was recently codified and expanded in the 21st Century Cures Act and renamed the “Breakthrough Device” program.¹⁸

Pediatric Studies

With respect to data for pediatric uses of medications, the Best Pharmaceuticals for Children Act allows for sponsors to be granted six months of market exclusivity should they conduct pediatric clinical trials on medical products already on the market upon written request from FDA.¹⁹ After the sponsor agrees to the written request and satisfies its requirements, an FDA review board makes a decision whether to grant the additional market exclusivity.

Current FDA Practice Related to Transparency

With some limited exceptions, FDA does not disclose information about the application process for a new medical product until — and if — the product is approved. The FDA’s current regulations prohibit contemporaneous disclosure of such milestones as the filing of application about human testing, the agreement on a Special Protocol Assessment, the filing of the marketing application, and whether products are receiving expedited review.²⁰

The most common exception to non-disclosure rules is when FDA convenes an advisory committee to consider specific questions related to a marketing application before FDA makes a final decision

whether to approve the application. The advisory committee meets in public and considers information in the application.²¹ Minutes of the advisory committee meetings are then posted on the FDA website.²²

The 1983 Orphan Drug Act requires FDA to disclose publicly when a drug qualifies for this program at the time of designation.²³ FDA discloses the proposed indication or intended use of the drug, and the date it was designated, but if the drug is at an early stage, it may only have a chemical or technical name, which will be uninformative to the general public.²⁴ Moreover, FDA does not disclose the name of the sponsor or the justification for the orphan drug designation.

lic filings with the Securities and Exchange Commission events that are “material” to the sponsor, which in some circumstances may include regulatory decisions by FDA. Of note, an event that might be material to an emerging biotech company with a single product in Phase 1 development might not be material to a large biopharmaceutical company. Many pharmaceutical companies subscribe to these databases, and several vendors report filling in “missing” (or otherwise not publicly reported) data based on direct feedback from sponsors themselves. Independent audits have found that the largest of these databases are likely to be comprehensive representations of the above information with respect to innovative product development.²⁸ Members of the public who cannot afford a subscription do not have access to the information within these commercial databases.

While FDA does not disclose information about key milestones in product regulation prior to approval, the European Medicines Agency publishes information at many key milestones in product regulation.²⁹

Modernizing FDA practices would bring benefits to patients, researchers, and investors in new products. The FDA Transparency Task Force’s recommendations from 2010 are an important starting place.

With respect to pediatric exclusivity, the Best Pharmaceuticals for Children Act includes provisions that provide public access to information regarding written requests, safety reviews, labeling changes, and other topics.²⁵ There is no requirement that FDA’s written requests be made available at the time of request.

Opportunities to Enhance Transparency at FDA

In its 2010 Report, FDA’s Transparency Task Force noted that greater transparency about the application process would be expected to promote participation in clinical trials, greater understanding of the regulatory process, and progress in developing new and innovative therapies for patients. The Task Force then proposed disclosing basic information about investigational applications, including the name of the application sponsor, the date the application was received, the proposed indication or intended use, and the proposed proper or trade name, if available. The Task Force also proposed disclosing the fact that a study has been placed on hold, and basic information about applications at the time of submission.²⁶

Much of this information is already being made available to those who can afford to license it. Commercially available services offer information to their subscribers about investigational applications and product filings.²⁷ These services draw upon a variety of public and proprietary sources. For example, a sponsor that has issued securities subject to the federal Securities Exchange Act of 1934 is obligated to disclose in pub-

Modernizing FDA practices would bring benefits to patients, researchers, and investors in new products. The FDA Transparency Task Force’s recommendations from 2010 are an important starting place. As the Agency noted then, it is of keen interest to those suffering from or studying a disease with limited available treatment to know whether and when a new drug, biologic, or device enters the clinical testing phase of development, and whether and when a marketing application is submitted. Greater disclosure will allow the financial markets to be aware of the progress of therapies through the review process without having to rely on company disclosures alone.

Beyond these recommendations, five additional types of disclosures have merit:

- **Mechanism of action or class of medical product.** There is substantial value to patients and researchers to understand the type of product under study, beyond just the sponsor’s assigned name and the particular use.
- **Link to ClinicalTrials.gov.** Adding the relevant National Clinical Trials number to disclosures by FDA will allow the public to understand the connection between clinical research and the regulatory process.
- **Whether and why a product has been assigned to an expedited development or review pathway or has been classified as an orphan drug.**

Greater transparency on this part of the regulatory process will allow patients to know which products are expected to provide a meaningful improvement over current treatments, which may, for example, stimulate enrollment in clinical trials for these products. Transparency will also provide policymakers with more opportunities to identify the strengths and weaknesses of these review pathways.

- **Safety or efficacy reasons for a clinical hold.** Patients, clinicians, and investigators can benefit from understanding why a study may be put on a clinical hold, and why the hold was lifted, especially if those reasons relate to patient safety.³⁰ Relying on companies alone for this information, which is now the case, means that FDA's rationale for the clinical hold remains obscured.³¹ When a clinical hold is based on safety or efficacy grounds, disclosure of the FDA perspective would best help patients and clinicians understand potential risks in other studies of drugs in the same or a related class and help investigators better appreciate obstacles that may affect the development of alternative products.
- **Special Protocol Assessments related to safety and efficacy.** Disclosure of these provisions can provide investigators with critical insight into the type of testing that can be used to gain approval of new products.

- **Written requests for pediatric studies.** Disclosure of FDA's written requests for pediatric studies under the Best Pharmaceuticals for Children Act at the time the written request is made by FDA can provide pediatric patient advocates and researchers with a better understanding of FDA's approach to needed pediatric studies. FDA should also disclose documents that memorialize acceptable changes to the initial request.³²

FDA Should Disclose More of Its Own Analysis and Decision-Making

Background

FDA's analysis and decision-making is considered by many to be the global gold standard in medical product regulation. This respect derives from the expertise of FDA review staff and the Agency's unique practice of reviewing individual-level patient data from clinical studies.

When FDA receives a marketing application, it conducts a threshold review of the application. If the application is incomplete, or if it is patently unapprovable, FDA notifies the sponsor by letter that the application will not be filed in its current form.³⁴

If FDA decides to review an application, it conducts a series of detailed assessments including re-analysis of raw data from applications in assessing whether products are appropriate for marketing to patients. These include chemistry, clinical, pharmacological, and statistical reviews.

Recommendations to Enhance FDA Transparency about Key Milestones in the Application Process

1. FDA should adopt the 2010 draft proposals of the Transparency Task Force on investigational applications, marketing applications, and the existence of clinical holds.³³ These proposals would make the basic information in these filings broadly available.
2. FDA should include in disclosures of investigational applications and marketing applications the class of medication and mechanism of action, if known. This should apply to supplemental New Drug Applications and Biologics License Applications for new indications.
3. FDA should include in disclosures of investigational applications and new applications the National Clinical Trial numbers for all trials conducted for marketing approval.
4. If FDA enters into a Special Protocol Assessment, FDA should release the text relevant to safety and efficacy after the study is completed.
5. When FDA has issued or released a clinical hold related to safety or efficacy, the FDA should release a summary of the reasons within 10 days.
6. FDA should disclose whether a marketing application has been designated for an expedited development or review program and, if so, the scientific basis for that designation. For orphan-designated drugs, in addition to disclosing the name of the drug and its proposed indication, FDA should also disclose the name of the sponsor and the epidemiologic basis for the designation.
7. FDA should disclose written requests for pediatric studies under the Best Pharmaceuticals for Children Act at the time such requests are made, as well as other documents indicating agreement on changes to the initial request.

FDA currently approves nearly all complete drug applications on the first cycle of review. Some unapproved applications require more information or have flaws that are then fixed by the sponsor, leading to an approvable application on a second review cycle. Others may be abandoned or withdrawn by their sponsors.

FDA conducts targeted analysis on medical products after marketing. These studies may be limited to one product or assess the profile of a group of products. To conduct these analyses, FDA has access to high-quality clinical data on safety and effectiveness, and FDA scientists often conduct extensive meta-analyses of these data. In the course of such analyses, FDA has created pooled data sets. For example, FDA scientists pooled data from 18 clinical trials (including 3 pediatric trials) to investigate the optimal time to measure detection of hepatitis C virus. The Agency found that future studies could use earlier endpoints for detection of the virus, reducing the expense and time for such research.

Current FDA Practice Related to Transparency

For public advisory committee meetings during the initial approval process and after products are approved as part of FDA's "action package,"³⁵ FDA releases most information about its analysis and decision-making. For supplemental indications, FDA releases its memos under the Freedom of Information Act and posts the memos if three requests are received.³⁶

In other circumstances, however, little is released. FDA does not release letters indicating that applications are not ready to be filed. Absent a public advisory committee meeting, FDA generally does not release its internal reviews for unapproved products.

WITHDRAWN APPLICATIONS

If a sponsor withdraws a marketing application before FDA acts on it, FDA does not release its reviews.

ABANDONED APPLICATIONS

If a sponsor ceases work on a pending New Drug Application, FDA may deem the New Drug Application to have been abandoned. In these cases, the Federal Food, Drug, and Cosmetic Act requires FDA to disclose "upon request" the clinical data contained in the abandoned or terminated New Drug Application.³⁷ FDA, however, does not disclose which New Drug Applications have been withdrawn, or that FDA considers to have been abandoned; there is also a lack of clarity on how manufacturers or the FDA define abandonment in this context.³⁸ FDA does not generally provide its perspective on whether the product was abandoned for scientific or non-scientific reasons.

NON-APPROVAL

When FDA declines to approve an application, the reviews are not typically released. When FDA approves a marketing application, the sponsor is notified by letter, and these approval letters are released to the public. However, after review, if FDA declines to approve the marketing application, the sponsor is notified by letter but FDA does not make this communication public.³⁹

Some FDA analyses are released to the public as part of safety communications or through scientific publication. However, FDA does not release the special data sets created for these analyses, even in masked and de-identified form.

Opportunities to Enhance Transparency at FDA

Noting the substantial value to science of more full explanations of drug withdrawals or regulatory non-approvals, the FDA Transparency Task Force in 2010 proposed releasing certain relevant Agency documents. These included the Agency's perspective on the safety of withdrawn applications, the Agency's perspective when a sponsor withdraws an orphan drug application for reasons other than safety (such as for business reasons), and the Agency's letters to drug, biologic, and device sponsors when their products are not approved.⁴⁰

The case for disclosing these communications was strengthened by a study published in 2015 by Lurie and colleagues at FDA. The study compared sponsors' press releases addressing FDA non-approval of their products with the content of the actual FDA letters.⁴¹ Their results showed striking disparities between FDA's grounds for deciding not to approve applications and the sponsors' explanations to their investors and the public. Thirteen press releases captured in the study did not include any of FDA's actual reasons. Thirty-two of FDA's letters in the study called for new clinical trials for safety or efficacy, but only 19 press releases mentioned this information.⁴² Seven of FDA's letters noted higher mortality rates in patients receiving the active treatment; only one press release included FDA's concern about higher mortality. In 11 cases, the company did not issue a press release about the non-approval.

The European Medicines Agency releases a European Public Assessment Report for "every human... medicine application that has been granted or refused marketing authorization."⁴³ This includes the agency's rationale for rejecting applications, where applicable. In some instances, the European Public Assessment Report may contain detailed information on the grounds for denying marketing authorization.⁴⁴

In a 2013 notice in the *Federal Register*, FDA proposed disclosing another type of analysis: the pooled data sets compiled by the Agency, albeit in masked and de-identified form. In making this proposal, FDA noted that: “These data have a tremendous potential to help address critical challenges and provide new opportunities for innovation in medical product development.”⁴⁵ The proposal received support from such organizations as the Cystic Fibrosis Foundation, Lupus Research Institute, the American Society of Clinical Oncology, and the Association of American Medical Colleges. Industry commenters included a broad range of views. Some expressed concern about permitting open access to the information, and others raised a range of logistical and legal considerations.

There are multiple benefits to greater transparency about FDA review, analysis, and decision-making. Transparency allows patients, researchers, and others to learn what the Agency thinks about products under review, including the real reasons why products were not approved. The clinical community can benefit from the insight, expertise, and analyses of FDA reviewers, and researchers can learn from the failures of previous medical products in subsequent research programs. The disclosure of FDA reviews for initial approval provides significant insight about the products; the disclosure of FDA reviews for supplementary indications at the time of their approval does the same. Advocates for patients with rare diseases have special reason for knowing when drug applications are withdrawn for reasons other than safety, so that other sponsors can be encouraged to take over the development process.

Important progress would be made by adopting FDA’s Transparency Task Force proposals related to drug withdrawals and Complete Response Letters from the FDA to sponsors.

The FDA’s 2013 proposal would allow researchers access to the pooled data sets that underlie internal FDA analyses. These data sets would be virtually impossible for researchers outside FDA to duplicate, because doing so would require separate agreements with all sponsors of the original research.

While there was support among researchers, patient groups, and some in industry for the FDA’s proposal, there was also widespread concern that overly broad distribution of the special data sets might threaten confidentiality and undermine the quality of research. An alternative approach would rely on existing mechanisms to make such datasets available to the medical and research community for purposes of creating or materially enhancing generalizable scientific or medical knowledge, with tight controls on privacy. As one illustrative example, the National Institutes of Health has established a Biologic Specimen and Data Reposi-

tory⁴⁶ with established procedures for de-identification of data and sharing data with responsible researchers for legitimate scientific investigations.⁴⁷ There are other examples of private and public clinical trial data repositories that could also be adopted for this purpose.

On the issue of abandoned applications, FDA’s issuance of bright-line guidance for industry on the circumstances that would constitute abandonment of an application would clarify when materials could be made available. For example, FDA might state that where no substantive progress has been made on an application for one year and without a detailed, factual explanation from the sponsor, FDA will consider the application to have been abandoned.

Recommendations to Enhance Transparency about FDA Analysis and Decision-Making

8. FDA should adopt the draft proposals from the 2010 Transparency Task Force that would provide information and explanations for withdrawn medications and would disclose FDA’s communications to companies when products are not approved.⁴⁸
9. FDA should make public its clinical and statistical reviews pertaining to products that are not approved or for which the marketing applications are abandoned or withdrawn. FDA should issue guidance on the definition of abandonment for the purpose of transparency.
10. FDA should make its pooled data sets, masked and de-identified as appropriate, and FDA’s analyses of these data sets, available to the medical and research community through clinical data repositories, such as through the National Institutes of Health Biologic Specimen and Data Repository Information Coordinating Center.

FDA Should Disclose More about the Review Process for Generic Drugs and Biosimilars

Background

In addition to its central role in the regulation of new therapies, FDA is the critical gateway to the market for thousands of generic drugs. In 2014, 88% of retail prescriptions in the U.S. were filled with generic drugs.⁴⁹ Manufacturers of generic drugs submit Abbreviated New Drug Applications that include a demonstration of bioequivalence between their product and the original drug.⁵⁰

In recent years, however, competition has declined in some corners of the generic market. Products that have only one or two manufacturers have become targets for companies with business models that involve finding monopoly markets and putting forward large price increases.⁵¹ There are additional scientific challenges

in creating bioequivalent products for certain types of therapies that compromise the ability of generic companies to navigate the FDA approval process successfully.

FDA also has authority, first granted by Congress in 2010 as part of the Affordable Care Act, to license follow-on versions of biologic products that are “highly similar” to, or “interchangeable” with, a previously licensed reference biologic product.⁵² Congress modeled this “biosimilars” legislation on the 1984 Hatch-Waxman Act that created an effective pathway for FDA to approve generic drugs.

Current FDA Practice Related to Transparency

FDA generally does not release information on which companies have filed generic drug applications, and for which drugs.⁵³ When FDA does not approve an application for a generic drug, the FDA does not release copies of “complete response” letters to industry, including those that provide details on failures of bioequivalence testing. FDA also does not release information on the submission of licensing applications for biosimilars.

Opportunities to Enhance Transparency at FDA

In 2010, the FDA Transparency Task Force recommended disclosing the name of the generic drug application sponsor and the name of the reference drug to be copied at the time the application is received.⁵⁴ The Transparency Task Force also considered whether to recommend release of letters to generic companies outlining why their products were not approved. The Task Force declined to support disclosure of such letters on the grounds that the reasons “primarily relate[] to how the drug was made, or to labeling negotiations between the sponsor and FDA” and the letters “contain[] a great deal of trade secret information.” The Task Force found “disclosing these letters would provide little insight about the rationale underlying FDA’s drug review process...particularly in light of the need to protect trade secret information.”⁵⁵

Recent examples of generic drugs becoming the subject of extremely high price increases have renewed interest in transparency. During investigation of these episodes, the public often wants to know whether competing products are in the pipeline. Yet, such information is unavailable. Without transparency, policymakers have been unable to determine how much of the problem is too little interest in joining the market and how much is due to other factors, such as historically extended review times for pending applications. This challenge speaks to the value of rapid disclosure of which drugs are in the application queue, as proposed by the Transparency Task Force.

FDA’s review of bioequivalence has also been propelled into the spotlight of late as a result of the con-

troversy over rising prices for the allergy medication epinephrine autoinjector (EpiPen). Teva Pharmaceuticals failed to bring to market a generic version, apparently due to challenges involved in making a bioequivalent delivery device for the epinephrine.⁵⁶ However, the FDA’s communication with Teva regarding these challenges was not disclosed. In the absence of disclosure, some commentators have blamed FDA for setting unreasonable standards for bioequivalence.⁵⁷

This example illustrates the value of disclosing those portions of the Complete Response Letters from FDA to generic manufacturers that relate to scientific issues of bioequivalence. Doing so would permit policymakers, patients, researchers, and others to understand why products were not approved and accelerate learning in the generic industry about key challenges and solutions. It would require redaction by FDA of trade secret information and a corresponding recognition that the Agency would not be disclosing problems related to the manufacturing process.

Biologic products are high-cost products, but can also provide innovative and effective new therapies. The filing of biosimilar licensing applications presents a compelling case for disclosure. Information on FDA’s assessment of biosimilarity will also be valuable for the more rapid development of other biosimilar products. Here, too, it must be recognized that FDA will not disclose information on the manufacturing process, which might be a major reason for non-approval of biosimilars.

Recommendations to Enhance Transparency Related to Generic Drugs and Follow-on Biologics

11. FDA should adopt its 2010 Transparency Task Force proposal to disclose the filing of generic drug applications, including the name of the sponsor and the name of the reference drug to be copied.⁵⁸
12. FDA should routinely disclose those portions of Complete Response Letters to generic drug manufacturers that relate to bioequivalence (as compared to manufacturing processes).
13. FDA should routinely disclose the filing of abbreviated biologics licensing applications, including the name of the sponsor, the reference biologic product, and whether the application is for “biosimilarity” or “interchangeability.”
14. FDA should routinely disclose those portions of a Complete Response Letter with respect to a biosimilar licensing application that relate to the biosimilarity to or interchangeability with the reference biologic product.

FDA Should Correct Misleading Information in the Market

Background

At times, companies and researchers may release information about the review process that may mislead physicians, patients, investors, and others about data submitted to the Agency or the Agency's perspective on product development.

For example, in March 2015, Orexigen, the sponsor of bupropion-naltrexone, a drug under development for obesity, filed a report with the Securities and Exchange Commission about a patent claiming that an as-yet unpublished safety study had a "positive

cant announced the post-hoc results, generating considerable public attention."⁶¹

The problem of misleading or inaccurate claims made by manufacturers may grow worse as a result of a recent appellate court decision that used the First Amendment protection of commercial speech as a justification for giving broader deference to companies to make statements about non-FDA-approved uses of available products.⁶²

Current FDA Practice Related to Transparency

As practice now stands, companies have wide latitude to characterize data submitted to FDA or their

The problem of misleading or inaccurate claims made by manufacturers may grow worse as a result of a recent appellate court decision that used the First Amendment protection of commercial speech as a justification for giving broader deference to companies to make statements about non-FDA-approved uses of available products.

effect...on [cardiovascular] outcomes" that "appears to be unrelated to weight change." This statement, however, misstated the evidence and did not reflect FDA's perspective. The Agency continued to require an additional study of cardiovascular safety of the medication.⁵⁹

In the case of eteplirsen (Exondys 51), a treatment for Duchenne muscular dystrophy, the randomized, placebo-controlled pivotal trial conducted in 12 patients for regulatory approval showed no advantage in the 6-minute walk test capacity of treated patients compared to those initially given placebo. However, post-hoc calculations excluding two of the eight eteplirsen-treated patients who deteriorated sharply found a statistically significant advantage for the remaining treated patients.⁶⁰ This post-hoc analysis was highlighted in the graphic display of this finding in the 2013 paper and in the manufacturer's press release announcing the success of the trial. Three years later, FDA revealed that these positive public announcements starkly contrasted with the undisclosed advice that FDA at the time gave the sponsor about the validity of the results and the potential for these data to support drug approval. As the lead reviewer stated in the Advisory Committee meeting, "FDA explained that these types of changes did not appear reasonable, even for hypothesis generation, and that the post-hoc analyses were not interpretable. However, the appli-

engagement with the FDA without the risk that FDA will correct the record. Under current regulations, FDA has the authority to correct such misconceptions only when doing so allows the Agency "to pursue its regulatory activities without disruption."⁶³ In practice, FDA rarely takes such action.

Opportunities to Enhance Transparency at FDA

FDA's 2010 Task Force Report recommended that FDA disclose relevant summary safety and efficacy information from an investigational application or a pending market application if the Agency concludes that disclosure is in the interest of public health. In taking this position, FDA noted that "selective publication of clinical trials results has, in the past, created a misleading picture of the safety and efficacy of a product, with negative implications for the public health. This is particularly pronounced when the product is used off-label (*i.e.*, for indications that have not been approved by FDA)."⁶⁴ It was further recommended that FDA correct misleading information about the product that is the subject of the application.⁶⁵

There are three relevant policy questions to FDA's ability to correct misinformation. The first is whether the Agency should adopt a basic set of standards for when to correct misinformation in the market. The advantage of doing so is to facilitate Agency engagement when needed without the worry of potential precedent set by each case. The Agency might con-

sider adopting a standard based on whether the information has the potential to cause significant confusion in the medical community and among patients about the safety or efficacy of a medical product for approved or unapproved uses. Even with such a standard, FDA should retain the authority to release information under other circumstances vital to public health.

The second question is whether the Agency should give advance notice to the company regarding any concerns. While this is reasonable as a matter of practice, FDA must remain able to move quickly to protect patients in response to urgent public health needs. An opportunity to provide advance notice should not lead to unnecessary delay.

The third question is whether FDA should disclose the scientific information that is the basis of its concern about misinformation in the market. Doing so would facilitate greater understanding of the Agency's position.

The FDA's Transparency Task Force was prescient in recognizing the potential danger of misinformation to public health. To prevent future harm from selective disclosures about the regulatory process by industry, FDA should adopt its 2010 proposal, making clear that it also covers misrepresentations about sponsor-FDA interactions. This will help the Agency protect patients, clinicians, researchers, and others from misleading information.

Recommendations on Correcting Misleading Information in the Market

15. FDA should establish a standard for correcting misleading information where there is the potential for substantial confusion about the safety and efficacy of the medical product for both approved and unapproved uses. The Agency should retain the ability to provide disclosures under additional circumstances vital to public health. To the extent feasible, FDA should provide advance notice to companies. FDA should also disclose the scientific basis for its concerns where possible.

FDA Should Disclose Data from Scientific Studies to Enhance Understanding of Medical Products

Background

During the development process, clinical trials generate extensive information about the safety and effectiveness of new and existing medical products. In support of a marketing application, sponsors are required to provide to FDA the investigational data collected dur-

ing the clinical trial phase. This information includes:

- **Patient-level datasets.** Sponsors provide raw data files for clinical trials to FDA for analysis. These files contain identifiable information.
- **Clinical Study Reports.** A Clinical Study Report is a comprehensive description and analysis of a clinical investigation conducted on humans, often requiring thousands of pages.⁶⁶ The Clinical Study Report generally provides summary information, but will include patient level data to address key questions.
- **Other postmarketing reports.** For drugs and biologics, FDA is authorized in specific circumstances to require sponsors to conduct post-approval studies (Postmarket Requirements).⁶⁷ In other circumstances, a sponsor may make a commitment to FDA to conduct post-approval studies (Postmarket Commitments).⁶⁸ Similarly, for certain devices, FDA may require post-approval studies.⁶⁹ These post-marketing studies may include clinical trials and observational studies. A post-marketing clinical trial will generally be reported to FDA in a Clinical Study Report. Reports on observational studies will be provided in alternative formats to the Agency.

Current FDA Practice Related to Transparency

FDA generally does not disclose patient-level datasets, Clinical Study Reports, or other postmarketing reports provided by sponsors.⁷⁰ FDA has taken the position that non-summary reports of clinical or pre-clinical studies are confidential commercial information and may not be disclosed by FDA, unless the information has been previously disclosed or acknowledged by the sponsor or others.⁷¹

The 2010 Transparency Task Force proposed that FDA convene a group of stakeholders to discuss the possible disclosure of non-summary data contained in product applications, but did not make specific proposals with respect to Clinical Study Reports or Phase IV studies.⁷²

Opportunities to Enhance Transparency at FDA

In recent years, there has been important evolution in thinking about access to data from clinical trials. In a recent report, the Institute of Medicine called on key stakeholders to "foster a culture in which data sharing is the expected norm, and...commit to responsible strategies aimed at maximizing the benefits, minimizing the risks, and overcoming the challenges of sharing clinical trial data for all parties."⁷³

Some pharmaceutical companies, such as GlaxoSmithKline and Johnson & Johnson, have taken leading roles in enabling independent investigators to submit requests to access some clinical trial data, subject to certain conditions.⁷⁴ One repository of the clinical trials for which investigators may request access is the Clinical Study Data Request website.⁷⁵ This trend is a valuable step toward greater transparency, but there is evidence that many more clinical trials are being conducted by industry than are being shared through websites such as these.⁷⁶

In October 2014, the European Medicines Agency adopted a new policy on disclosure of Clinical Study Reports submitted in marketing applications after January 1, 2015.⁷⁷ In October 2016, the agency, pursuant to this policy, for the first time posted on its website approximately 260,000 pages of detailed clinical trial data and information on two drugs (carfilzomib and lesinurad) that it had recently approved. These pages were posted with only minimal redactions to protect patient privacy and confidential commercial information. The agency plans to eventually release clinical data within 60 days after approval, or 150 days after a marketing application is withdrawn. In December 2016, the agency published detailed guidance on its publication of clinical data, including permissible redactions.⁷⁸ There is a pending legal challenge in the European Union to the agency's disclosure of clinical trial data that could eventually affect implementation of the disclosure policy.⁷⁹

The sharing of clinical trial data will advance innovation, improve clinical study design, and avoid exposing humans to trials of products that have already failed to meet pre-specified endpoints or caused harm. In the case of observational post-approval studies, while some are published, a policy of transparency will improve the assessment and surveillance of the known and unexpected serious risks to patients related to the use of the drug, biologic, or device.⁸⁰

With respect to data sets with individual patient data, there are important privacy concerns that must be addressed. As noted above, the National Institutes of Health has established Biologic Specimen and Data Repository Information Coordinating Center,⁸¹ a repository with established procedures for de-identification of data and sharing data with responsible researchers for legitimate scientific investigations.⁸² There are other examples of private and public clinical trial data repositories that could also be adopted for this purpose, each of which take advantage of various safeguards to promote the sharing of clinical research data to advance science and improve public health and healthcare; promoting the responsible conduct of

research; ensure good stewardship of clinical research data; and protect the rights of research participants.

With respect to Clinical Study Reports, there is value in developing and harmonizing FDA policy with that of the European Medicines Agency. Sponsors often submit essentially the same data and analyses to the European Medicines Agency, FDA, and similar medical product regulatory agencies around the world. Many nations follow the lead of these regulatory authorities. The European Medicines Agency's Policy 0070 provides an opportunity for FDA to develop a coordinated policy that provides efficiency and certainty to industry and transparency for the public.

Similar standards could then be applied to reports of observational post-approval studies.

Recommendations on Disclosure to Enhance Scientific Understanding

16. FDA should disclose online Clinical Study Reports that have been submitted to FDA in support of a marketing application after approval of that application, or after issuance of a Complete Response Letter, or upon the withdrawal or abandonment of the application. This disclosure should include the applicable ClinicalTrials.gov numbers. FDA should consider using a data repository, such as the National Institutes of Health Biologic Specimen and Data Repository Information Coordinating Center as an intermediary to protect patient privacy. To the extent possible, FDA should harmonize standards on Clinical Study Reports release with the European Medicines Agency.⁸³
17. FDA should release the final reports that fulfill Postmarketing Requirements and Postmarketing Commitments, including Clinical Study Reports of Phase IV Studies and other post-approval reports, at the time FDA considers the sponsor's obligation to conduct a study to be fulfilled. This disclosure should include the applicable ClinicalTrials.gov numbers, if any. FDA should consider using a data repository such as the National Institutes of Health Biologic Specimen and Data Repository Information Coordinating Center as an intermediary to protect patient privacy.
18. When there are clinical trial data, including patient-level data, that were submitted to FDA in support of a marketing application but that are not reasonably available to independent investigators through industry-sponsored websites, then FDA should make data available, such as through the National Institutes of Health Biologic Specimen and Data Repository Information Coordinating Center, with policies on de-identification to protect patient privacy.

Responses to Potential Objections

Supporters of transparency at FDA include families looking to understand the progress of potential new treatments, researchers in search of understanding to develop better therapies and cures, investors in need of greater certainty about the regulatory process, companies that would like to better predict how FDA will react to their product applications, and clinicians seeking more data and analysis to improve patient care. Despite great interest, progress in transparency at the Agency has been slow. In this report, we outline the case for change by focusing on those items with the greatest promise for medical innovation. We are aware, however, that some may raise questions and concerns about what we have recommended.

One potential objection to the Report's recommendations is that greater transparency will undermine the business case for innovation. The concern is that if information or analysis related to one company's products is available to help competitors, there is less likelihood that the company will proceed in the first place. In 2009, PhRMA responded to FDA's Transparency Task Force Report, in part, by supporting greater explanation of FDA decision-making. However, the organization expressed concern about release of information submitted by companies, writing, "If FDA were to disclose this information prematurely, sponsors could be motivated to avoid such voluntary information sharing. This, in turn, could negatively affect FDA's regulatory decision-making abilities."⁸⁴

Many of our recommendations do not bear on PhRMA's central concern. Basic information about the regulatory process is already broadly available through proprietary databases; FDA disclosure will create a level playing field and improve access to information for the public. Greater disclosure of FDA analysis and decision-making will create new opportunities for companies to be successful with the Agency. Targeted disclosures to correct misinformation are necessary to avoid market confusion. In other recommendations, we have paid special attention to the nature and timing of disclosures to minimize the risk that may be of greatest concern to manufacturers. For example, we recommend releasing only information about clinical holds and Special Protocol Assessment provisions on safety and efficacy, not other topics that are more likely to touch on actual trade secrets. Our recommendation on release of scientific data submitted by companies for clinical studies focuses on those where sponsors have not already made their data available by other means.

A related potential objection relates to the potential disclosure of non-approval documents such as Complete Response Letters, which set out why FDA failed

to approve or clear a medical product. Companies that fail once but plan to try again may consider release to be premature disclosure. Yet at this early stage, for innovator drugs, patent and data exclusivity protections still apply. The release of the letter serves to inform patients, doctors, investors, and others of the regulatory status of the product and to help researchers understand the potential limitations that need to be overcome in creating safe and effective alternative products. For generic products, the letters' findings on bioequivalence (which are the only portions we recommend making public) are unlikely to give a competitor a short-term edge, but over time could prevent substantial wasted effort by other companies. Since the generic industry includes many companies who compete on many products, disclosure of issues of bioequivalence, over time, will likely help all of them succeed.

A skeptic might ask whether additional transparency is needed. That is, if FDA knows about the benefits and risks of products, is it not enough for the Agency to pass that knowledge along through the review process? For example, if one product failed because of problems with kidney toxicity, the Agency might require additional kidney testing for other similar products.

FDA does, in fact, play exactly this role today. The regulatory process, while important, represents only a fraction of the potential space where this information may be useful. Broader transparency can empower patients, clinicians, researchers, and others to use information more effectively for a broad range of goals. For example, knowledge that a product failed because of problems with kidney toxicity may help patients and clinicians to understand the need for alternatives and lead researchers to focus on new assays of kidney function or develop new compounds that work through different mechanisms.

With respect to correcting misinformation in the market, it is important to note that FDA cannot possibly police all statements by sponsors and others. Some may, therefore, point out that adopting the policy we recommend creates the risk that silence by the Agency will be publicly understood as agreement with whatever is being said. It will be important for FDA to dispel this notion. We do not believe the risk of this misunderstanding outweighs the benefit of clearing up substantial confusion about the safety and efficacy of medical products.

Transparency can be costly, and, if misapplied, can unnecessarily slow down regulatory decision-making. Most of our recommendations regarding transparency involve public dissemination of products that FDA has already created and that clearly does not involve

trade secrets or data that can lead to identification of patients (such as complete response letters or de-identified secondary databases), or basic information about regulatory milestones that should involve minimal resources. However, some of our recommendations would require more effort and resources on the part of the Agency. The most challenging are those that involve disclosure of large amounts of scientific data from clinical trials. These files are extremely large, and special care must be taken to protect patient

(thus preserving individual privacy) and publishing them through an existing federal repository, such as the National Institutes of Health Biologic Specimen and Data Repository Information Coordinating Center.

Any repository adopted for this purpose should employ safeguards to promote the sharing of clinical research data to advance science and improve public health and healthcare; promoting the responsible conduct of research; ensure good stewardship of clinical research data; and protect the rights of research

Following the path set out by this Blueprint for Transparency will take energy and persistence, but it is well worth it. Greater transparency at FDA will lead to safer and more effective medical products, with lasting benefits for clinical care, scientific progress, and public health.

privacy. In addition, based on comments submitted to FDA to date, it is likely the Agency would face legal challenges from manufacturers to such disclosures. While our view is that such challenges would not have legal merit, the legal process could be burdensome on the Agency. If the FDA agrees to take up these costlier recommendations, it should move forward with sufficient funding and with the legal support of the Administration and Department of Justice. Greater disclosure of scientific data can generate substantial value over time, in terms of scientific understanding and assistance for further product development, far more than the cost of disclosure.

Some may be concerned that FDA would go beyond our recommendations and disclose too much information. Our recommendations are for the Agency to set clear policies in these areas, not make ad hoc transparency determinations. In areas of Agency discretion, such as to correct misleading information in the market, we have recommended the Agency provide advance warning to product sponsors, if possible.

Others may be concerned about patient privacy. Patient privacy objections are most salient in the context of datasets with patient level information and Clinical Study Reports. The Report recommends that FDA permit the online release of redacted Clinical Study Reports, similar to the redacted Clinical Study Reports that are produced in response to Freedom of Information Act requests. Redacted Clinical Study Reports remove any identifying information about specific patients, including the part of the ID number that would reveal the site of the study. Similarly, the Report recommends that the FDA release redacted datasets per National Institutes of Health guidelines

participants. For instance, before releasing data, the repository should verify the research proposed would advance science or improve public health and healthcare, check institutional status, and create legally enforceable agreements that ensure applicants will not compromise patient identity.

Conclusion

Following the path set out by this Blueprint for Transparency will take energy and persistence, but it is well worth it. Greater transparency at FDA will lead to safer and more effective medical products, with lasting benefits for clinical care, scientific progress, and public health.

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2. See FDA’s Progress Report on the Transparency Initiative, available at <<http://www.fda.gov/AboutFDA/Transparency/TransparencyInitiative/ucm273854.htm>> (last visited July 12, 2017).
3. For example, in a case involving a request for clinical trial and related data for FDA approvals of sofosbuvir (Sovaldi[®], Gilead) and sofosbuvir/ledipasvir (Harvoni[®], Gilead) under the Freedom of Information Act, the FDA has produced thousands of pages of documents from clinical study protocols to adverse event data. See e-mail from Cortelyou C. Kenney, Counsel of Record in Treatment Action Group v. FDA, No. 15-cv-976 (D. Conn. Sept. 20, 2016), to Amy Kapczynski, Professor of Law, Yale Law Sch. (Oct. 25, 2016 04:26 EST) (on file with authors). FDA does not comment on ongoing litigation.
4. This paper does not cover many other possible issues of transparency at FDA. For example, it does not cover issues of transparency about disagreements within FDA, an area in which the Agency has made important progress in recent years. It does not cover transparency about FDA’s internal timelines. The paper does not address veterinary medical products, tobacco products, or food. It does not cover most communications between companies and FDA, including such industry submissions as Periodic Benefit-Risk Evaluation Reports and Periodic Safety Update Reports. In addition, the focus on a practical transparency agenda means that the members of the FDA Transparency Working Group may individually support additional recommendations for transparency not included in this paper.
5. FDA’s definition of trade secret is: “A trade secret may consist of any commercially valuable plan, formula, process, or device that is used for the making, preparing, compounding, or processing of trade commodities and that can be said to be the end product of either innovation or substantial effort. There must be a direct relationship between the trade secret and the productive process.” 21 C.F.R. 20.61(a).
6. The report’s recommendations aim to improve proactive disclosure of information by FDA. As a result, the report does not specifically address implementation at FDA of the Freedom of Information Act, a law that provides the opportunity for citizens to request information. In general, FDA policies and regulations that limit proactive transparency also limit the Agency’s ability to share information in response to a request under the Freedom of Information Act.
7. The relevant regulations include: 21 C.F.R. §312.130(a) (non-disclosure of Investigational New Drug applications for drugs); §601.50 (non-disclosure of Investigational New Drug applications for biological products); §812.38(a) (non-disclosure of Investigational Device Exemptions applications); §314.430(b) (non-disclosure of New Drug Applications prior to approval); §601.51(b) (non-disclosure of Biologics Licenses Applications prior to approval); §814.9(b) & (c) (non-disclosure of Pre-Market Approval applications prior to approval); and §807.95(b) (non-disclosure of 510(k)s where the submitter of the 510(k) certifies that the submitter’s intent to market the device is confidential commercial information).
8. The ‘sponsor’ of a product subject to FDA regulation is usually the company that controls the rights to that product. A ‘biologic product’ generally is a type of drug that is produced from a biologic source, such as a living cell.
9. 21 C.F.R. §812.30 (IDEs), §312.40 (Investigational New Drug applications).
10. 21 C.F.R. §312.42(a) (“A clinical hold is an order issued by FDA to the sponsor to delay a *proposed clinical investigation* or to suspend an ongoing clinical investigation.” (emphasis added)).
11. FDCA §505(b)(5), 21 U.S.C. §355(b)(5).
12. Despite the difference in names, which exists for historical reasons, FDA’s review process is similar for both New Drug Applications and Biologics License Applications.
13. A PMA is “approved” by FDA; a 510(k) is “cleared” by FDA. Several factors, including the equivalence to previously approved devices and the risk of the device, determine whether a device requires a PMA or 510(k). For a low to moderate risk device where there is no existing predicate device that is not within a device type that is class III, a sponsor can submit a *de novo*.
14. FDA, *Guidance for Industry: Expedited Programs for Serious Conditions—Drugs & Biologics* (May 2014), available at <<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf>> (last visited July 12, 2017).
15. The Orphan Drug Act of 1983 (ODA) is codified as amended at FDCA §§525-529, 21 U.S.C. §§360aa-360ff. The ODA provides priority review only for potential treatments for rare pediatric diseases. FDCA §529, 21 U.S.C. §360ff. An orphan drug designation does not “alter the standard regulatory requirements and process for obtaining marketing approval.” FDA, *Designating an Orphan Product: Drugs and Biological Products*, available at <<http://www.fda.gov/forindustry/developingproductsforrareconditions/howtoapplyfororphanproductdesignation/default.htm>> (last visited July 12, 2017).
16. Pub. Law 114-255 (Dec. 13, 2016), §3033.
17. FDCA §515(d)(5), 21 U.S.C. §360e(d)(5); FDA, *Expedited Access for Premarket Approval and De Novo Medical Devices Intended for Unmet Medical Need for Life Threatening or Irreversibly Debilitating Diseases or Conditions: Guidance for Industry & FDA Staff* (April 13, 2015), available at <<http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM393978.pdf>> (last visited July 12, 2017).
18. Pub. Law 114-255 (Dec. 13, 2016), §3051.
19. FDCA 505A, 21 U.S.C. §355a.
20. 21 C.F.R. sec. 20.100 contains a list of specific FDA regulations that provide for non-disclosure of particular milestones in the regulatory process.
21. FDA proactively releases to the public the ‘background package’ that is provided to an advisory committee. 21 C.F.R. §314.430(d)(1) (disclosure of “selected portions of the safety and effectiveness data” in connection with advisory committee consideration of a New Drug Application); §601.51(d)(1) (similar provision for Biologics License Application advisory committees); §814.9(d)(1) (similar provision for Pre-Market Approval Application advisory committees); FDA, *Guidance for Industry: Advisory Committee Meetings — Preparation & Public Availability of Information Given to Advisory Committee Members* (August 2008), available at <<http://www.fda.gov/downloads/regulatoryinformation/guidances/ucm125650.pdf>> (last visited July 12, 2017).
22. Under federal law, FDA is not permitted to disclose trade secret information to advisory committees.
23. FDCA §526(c), 21 U.S.C. §360bb(c) (“Notice respecting the designation of a drug under subsection (a) [as an orphan drug] shall be made available to the public.”)
24. For example, on August 29, 2016, FDA designated a drug intended to treat neuroblastoma as an orphan drug. On FDA’s website, however, the drug was identified only as ‘131-I-8H9 monoclonal antibody.’ National Cancer Institute, Drug Dictionary: Iodine I 131 monoclonal Antibody 8H9,” available at <<https://www.cancer.gov/publications/dictionaries/cancer-drug?cdrid=380753>> (last visited July 12, 2017).
25. See FDA TTFR Draft Proposals at page 37. *Supra* note 1.
26. FDA TTFR Draft Proposals 8, 9 and 10. *Supra* note 1.

27. These include Informa PLC, IMS Health, Evaluate Group, Pharmaprojects, and Springer Nature.
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32. In addition to written requests for pediatric studies under the Best Pharmaceuticals for Children Act, FDA is authorized to require submission of pediatric study plans for new drugs and biologics under the Pediatric Research Equity Act. See FDCA §505B, 21 U.S.C. §355c. Others have recently called for these pediatric study plans to be made publicly accessible, as they provide important clinical information that can accelerate pediatric research and improve pediatric care. See F. T. Bourgeois and T. J. Hwang, "The Pediatric Research Equity Act Moves Into Adolescence," *JAMA* 317, no. 3 (2017): 259-260.
33. FDA TTFR Proposals 8, 9, and 10. *Supra* note 1.
34. Depending on the type of marketing application, these letters have different names (e.g., 'refuse to file' 'refuse to accept, not approvable, or denial). A different procedure is followed for 510(k)s.
35. FDCA §505(l)(2), 21 U.S.C. §355(l)(2).
36. Section 505(l)(2)(A) of the FD&C Act (21 U.S.C. 355(l)(2)(A)) states:
 "(1)PUBLIC DISCLOSURE OF SAFETY AND EFFECTIVENESS DATA AND ACTION PACKAGE
 ...
 (2)ACTION PACKAGE FOR APPROVAL.—
 (A)Action package.—The Secretary shall publish the action package for approval of an application under subsection (b) or section 262 of title 42 on the Internet Web site of the Food and Drug Administration—
 (i) not later than 30 days after the date of approval of such application for a drug no active ingredient (including any ester or salt of the active ingredient) of which has been approved in any other application under this section or section 262 of title 42; and
 (ii) not later than 30 days after the third request for such action package for approval received under section 552 of title 5 for any other drug."
 37. 21 U.S.C. §355(l)(1). This section outlines that 'safety and effectiveness' data included in a New Drug Application must be disclosed to the public when the New Drug Application has been abandoned, or FDA determines that the New Drug Application is not approvable, or FDA withdraws approval of the New Drug Application, or on the first date an Abbreviated New Drug Application using the drug covered by the New Drug Application as the Reference Listed Drug (RLD) could be approved. This provision is qualified, however, by the phrase: "unless extraordinary circumstances are shown."
 38. A. S. Kesselheim and M. M. Mello, "Confidentiality Laws and Secrecy in Medical Research: Improving Public Access to Data on Drug Safety," *Health Affairs* 26, no. 2 (2007): 483-491.
 39. In the case of an New Drug Application or Biologics License Application, this letter is known as a 'Complete Response Letter.' For pre-market approval, this letter is known as a 'Not to Approve Letter.' In the case of a 510(k), a different procedure is followed, and the letter is known as an 'Additional Informa-

tion Letter,' or 'Not Substantially Equivalent Letter' (NSE). The only time a Complete Response Letter is generally released is in the case that the product is eventually approved. On rare occasions, a Complete Response Letter may be disclosed as part of a background package for an advisory committee. Applications for Approval to Market a New Drug; Complete Response Letter; Amendments to Unapproved Applications. 73(133) FED. REG. 39588, at 39601 (July 10, 2008) (noting "our long-standing presumption that before approval or tentative approval, the existence of an application is confidential commercial information"). Not Substantially Equivalent letters and Additional Information letters are not released even if FDA eventually clears the device.

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63. 21 C.F.R. §20.82 (FDA Commissioner has discretionary authority to disclose any or all of a record otherwise exempt from disclosure if the disclosure is "in the public interest" and is necessary for the Agency "to pursue its regulatory activities without disruption." The regulation specifically exempts trade secrets and commercial or financial information that is privileged or confidential, any information for which disclosure would constitute a clearly unwarranted invasion of personal privacy, and any record that is prohibited from public disclosure by statute.) FDA might also consider taking enforcement action if the inappropriate comments represent misbranding under the Food, Drug, and Cosmetic Act.
64. FDA TTFR at 49. *Supra* note 1.
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Transparency at the U.S. Food and Drug Administration

Robert M. Califf

The U.S. Food and Drug Administration's (FDA) activities have enormous and wide-ranging effects on the economy and health of America and the world as a whole. The degree to which its activities should reflect an approach founded on complete transparency versus one focused on preserving confidentiality of information deserves public discussion. The current status quo reflects more than a century's accumulation of laws, regulations, guidances, court decisions, practical precedent, and philosophical tradition. However, given significant changes in the environment in which the FDA now operates, it is reasonable to critically examine the basis for current practices. The "Blueprint for Transparency"¹ calls for a host of specific actions to increase transparency across five major areas.

Achieving the right balance of transparency and confidentiality is a perennial concern for the FDA. On one hand, reasonable requirements for transparency are critical to stimulating effective innovation, dissemination of knowledge, and good business practice. On the other hand, ensuring the vitality of the medical products industry requires protecting legitimately proprietary information that forms the basis for investment in the development of such products. The authors of the Blueprint believe that emphasis on

the latter priority has gone further than necessary, to the detriment of public and individual health. They argue that greater transparency will have distinct benefits, including more evidence to inform practice and education, faster innovation enabled by widespread availability of knowledge about successes and failures, improvements in the FDA's internal processes resulting from the "sunshine effect," and greater public confidence stemming from an improved understanding of the agency's role and function.

Past interactions between the FDA and industry concerning specific medical products have included a minimal number of experts and have been conducted away from the public view except at prespecified times, such as advisory committee meetings or postings of product labels. This approach seems increasingly outdated in light of the information revolution and societal attitudes that value transparency as a desirable goal in itself. Further, such secrecy arguably impedes progress in therapeutic development and healthcare — progress that could be enabled with greater transparency and wider sharing of information. It is important to remember, however, that the FDA's current approaches reflect deeply ingrained precedents and are fundamentally grounded in the principle that protecting trade secrets provides incentive for investment in competitive businesses. Tensions arising from these issues will be addressed below for each of the Blueprint's main recommendations.

Interactions between the FDA and Industry During Product Development

The first area in the Blueprint recommendation concerns the disclosure of information exchanged between industry and the FDA about key product development milestones. It includes seven specific recommenda-

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tions, ranging from publicly acknowledging the existence of specific transactions (receipt of applications; existence of “clinical holds”) to the release of detailed product information that is not currently available. The primary counter-arguments for confidentiality in this context are based on the view that information about these milestones is either proprietary per se, or that the correspondence is so intertwined with trade secrets that releasing it publicly poses a risk of inadvertent disclosure that outweighs the benefits of transparency.

The degree to which communication between the FDA and industry is critical to rational and efficient medical product development is generally underappreciated by those who have not directly participated in this process. As government employees without financial conflicts, members of FDA review teams have access to key information about all ongoing development programs in a therapeutic area — including the programs of direct competitors of the product in question. Carefully crafted guidance in the context of specific product development can steer companies and researchers away from unproductive areas without revealing competitors’ trade secrets, or lead to critical investigation of issues about safety and mechanism of action that would not otherwise be known. During recent User Fee negotiations, holding more frequent meetings with FDA staff was a much more important goal for industry than was further expediting the review process — a clear indication of the value of these interactions.

One simple recommendation that would directly improve understanding about the risks and benefits of medical products is to ensure that FDA references to clinical trials are linked to their NCT numbers in the ClinicalTrials.gov registry. With the final rule for ClinicalTrials.gov completed,² a comprehensive approach to curating information about clinical trials, including their results, is emerging. Previous arguments against linking to NCT numbers as a matter of agency policy have reflected uncertainty about whether ClinicalTrials.gov would become the definitive source of information on the topic, as well as concerns that linking would imply FDA endorsement of the veracity and importance of the individual trial. Because ClinicalTrials.gov by design includes all qualifying trials regardless of quality, this concern is understandable, but facilitating access to relevant trial data is a much higher societal priority.

Increased Disclosure of Internal FDA Analysis

Recommendations for disclosing more of the FDA’s internal analyses and decision-making are likewise sensible. Participating in the Advisory Committee sys-

tem was a highlight of my early career as a researcher: it was initially startling to see the differences between what was reported in journals and the full scope of raw data from relevant clinical trials. I have personally disagreed with a minority of FDA analyses and interpretations, and internal disagreements within the FDA are not uncommon — this is the nature of science. Thus, FDA reviews for rejected, withdrawn, or abandoned products are potentially valuable for formulating alternative arguments about the appropriate interpretation of available data.

The remaining question concerns balancing the effects of such information on subsequent product development versus the clarity provided for research participants and their doctors about subsequent studies. Companies may be reluctant to go forward with product development if their errors and weaknesses are publicly displayed, or investors may withdraw support. On the other hand, making such data public could lead to new insights and enable researchers and study participants to make better choices.

While releasing information about non-approvals is sensible, several caveats apply. On a practical level, redacting sensitive information from these documents would require considerable effort and funding would need to be allocated. More importantly, it is critical to understand that non-approved applications comprise the tip of the iceberg in terms of preclinical and clinical data that are not shared openly. Because of the success of the “meeting system” between the FDA and industry, most products that are very likely to fail the review process are simply not submitted for review at all. This ability to “fail fast” prevents waste of time and resources and is good for patients, society, and investors. But because of the confidential approach and also because early-phase trials are exempt from registration requirements,³ most of the information from failed development programs never informs public scientific discourse.

Anyone who has been directly involved in medical product development knows that the degree to which companies reveal ongoing information to the FDA is variable. When the system is working well, more sharing is beneficial, because the agency can help inform decisions about product development that may have major effects on study participants or on investors. But if companies know that such information will routinely become public, they may be less inclined to share.

Pooled datasets from internal FDA analyses could be valuable, but these present interesting challenges, particularly when related to product safety. Academic authors are concerned about the proliferation of low-quality publications, and industry has legitimate con-

cerns about inappropriate analyses being conducted by people who lack important contextual knowledge.⁴ Industry, government, and academia are currently working to refine responsible approaches to sharing data from trials while protecting confidential patient information.⁵

Generics and Biosimilars

Increased transparency about the review process for generic drugs and biosimilars may also be warranted. Bioequivalence and interchangeability are complex concepts, and detailed guidance continues to evolve. Recent public confusion about the so-called generic “backlog”⁶ shows how partial reporting can lead to misinterpretation. The Blueprint authors argue that more public information about specific decisions on bioequivalence and interchangeability would help

requirement to register trials (and subsequently to report results). At every step, critics argued that transparency would reveal trade secrets and reduce competition, but there is no evidence that this has occurred. It is likely that if the “treasure trove” of highly curated trial data within the FDA were made more widely available, patients, academia, and industry would benefit from the increase in knowledge and the assurance that competition would not be diminished.

Confronting Misleading Information in the Public Sphere

I am unabashedly enthusiastic about the FDA responding proactively to misinformation in the public arena. When FDA precedents first developed, doctors were considered more authoritative and independent, and they obtained information about medical products

While primary data and information have value, as articulated by the Blueprint authors, much could be gained by more frequent updates from the FDA that synthesize what is known across major fields. Industry and academia need to understand not only what is known about a given therapeutic area, but also the FDA’s thinking about that field, because the agency has access to core information across the entire spectrum of technology development. Unfortunately, good guidance practice initiated to incorporate reliable processes into guidance construction has become cumbersome. The creation and implementation of more fluid methods for FDA review groups and their counterparts working on postmarket issues may be at least as useful as having patients, academics, and industry try to discern the most relevant information from raw data and correspondence.

industry devise better development programs, and the FDA is currently moving toward significantly greater transparency in situations where more competition is clearly needed.⁷ But whether releasing all applications would enhance rational competition and improve quality, or instead cause competitors to stay away out of concern for reputational risks, remains debatable.

Access to Raw Study Data

We have already witnessed major changes in transparency with the evolution of ClinicalTrials.gov, which was originally conceived to improve patient access to clinical trials. However, when concerns arose about industry sponsors suppressing results, medical journals required preregistration of trials as a condition of publication; this was followed by enactment of a legal

from sources such as print journals, regular professional meetings attended in person, and in-person visits from industry sales representatives. The Internet has radically changed this equation, and the FDA is only one voice amid a cacophony of information available to patients, families, and the health systems that now employ most doctors.

When the agency had more direct influence on advertising and sources of information were limited, it was sensible for the agency to “keep its powder dry” and work behind the scenes, resorting to legal action only when confidential communications failed. However, the recent affirmation of First Amendment rights for corporations⁸ has made it more difficult for the FDA to counter misinformation. Furthermore, direct-to-consumer advertising raises trou-

bling issues about the public risk posed by misleading information,⁹ and the Internet is rife with false or partially truthful claims. These issues become particularly acute with vulnerable populations participating in early-stage drug or device development, when information asymmetry exists because of industry use of press releases or nontransparent presentations that make claims that are known to be incorrect within the FDA. The agency should be more aggressive in identifying misleading or erroneous information in the public arena.

This proactive approach should not be taken lightly. Although I believe the FDA should have a stronger, more persistent public voice, if it fails to maintain a high standard, it could easily lose its current place as the most trusted source of reliable information about the benefits and risks of medical products.¹⁰ The Blueprint recommendations are sensible: develop standards, warn before acting, and then reveal the relevant information.

Alternatives to Consider

While primary data and information have value, as articulated by the Blueprint authors, much could be gained by more frequent updates from the FDA that synthesize what is known across major fields. Industry and academia need to understand not only what is known about a given therapeutic area, but also the FDA's thinking about that field, because the agency has access to core information across the entire spectrum of technology development. Unfortunately, good guidance practice¹¹ initiated to incorporate reliable processes into guidance construction has become cumbersome. The creation and implementation of more fluid methods for FDA review groups and their counterparts working on postmarket issues may be at least as useful as having patients, academics, and industry try to discern the most relevant information from raw data and correspondence.

Additionally, the FDA could provide concise summaries of key points when actions are taken in addition to the timelines of key milestones. This approach would avoid time-consuming redactions and enable the FDA to provide specific useful information to the field.

Conclusions

The overall goal of improving transparency by facilitating access to information is an excellent one. However, for each of the Blueprint's recommendations, an argument could be made that more transparency about the FDA's thinking and cumulative understanding of an issue, enabled by a more nimble guidance

process, may be just as important. The medical products industry differs from others in that more guidance from regulators is generally viewed positively, and the confluence of knowledge available when all stakeholders pool their experience, insight, and expertise is critical to developing effective pathways for better therapies. The extent to which these deliberations are informed by primary information that enables the broader community to form its own opinions versus the degree to which public access to this information will reduce competition by causing industry to withhold data or lose confidence in the protection of intellectual property that drives investment should be the determining factor. In the end, history is on the side of sunshine, and I advocate both greater transparency and more guidance from the FDA that clarifies its thinking to those engaged in developing products.

Note

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FDA Transparency in an Inescapably Political World

Daniel Carpenter

With multidisciplinary collaboration across four stellar institutions and with wise, forward-looking support from the Arnold Foundation, the Food and Drug Administration (FDA) Transparency Working Group has produced a thoughtful and useful report.¹ I congratulate the academics for having moved the debate forward and for having produced a nuanced and balanced, yet concise analysis that offers concrete, implementable recommendations.

I especially applaud the Working Group for their commendable focus on disclosure of information. FDA has a lot of information relevant to public health, and much more of it needs to be available to the public and to the American health system. In this respect, the report builds helpfully on important writings by Aaron Kesselheim and collaborators on the profound social costs of overly restrictive confidentiality requirements at the agency, whether in data that might assist drug development or drug safety monitoring.²

Yet what the public should see in a transparent agency is much more than what should get disclosed to patients, and transparency means much more than disclosure of data. Taking the term more literally (from the Latin verb *transpareo*), transparency implies that which “shines through” or “shows through” from an agency to its viewers. It means the ability to view the agency’s inside, to see across the border separating the public from the agency’s internal decisions.

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In this sense, there are aspects of the report that I find disappointing. The report consults neither the academic literature on transparency, nor the literature on industry influence in regulation, both of which are odd and unfortunate omissions. Much of that literature suggests that transparency and disclosure policies have uncertain effects, sometimes countervailing implications that undo their intent,³ and while I think that transparency is still worth the bargain and represents an important ethical commitment, the drawbacks of policy changes should be thoroughly considered.

Well beyond the issue of effectiveness comes the issue of industry and special interest influence upon FDA decision making. When ethicists, legal scholars, and public policy scholars discuss government transparency, they are usually interested in making sure that decisions taken under the auspices of sovereign power reflect the broad public interest and not a narrow special interest.⁴ Just as interest in transparency has risen, so too has interest in “capture” in the regulatory sphere, as witnessed by the General Accounting Office’s recent activity in investigating regulatory capture in U.S. financial agencies.⁵ The FDA is one of the most powerful agencies in the world,⁶ and concern about the economic and political power of the pharmaceutical industry is also growing.⁷ These concerns pertain not only to distribution of information about medical treatments, but letting the public see what is happening in the agency, as a check upon its decision making. We want to know this not only as patients, physicians, and scientists, but also and more importantly as citizens.

So while I generally laud the report, I think a truly meaningful approach to transparency of decision

making at the FDA needs to go further, take a broader view, and to consider what the stakes of transparency really are. Doing so need not restrict anyone to moves that can be administratively implemented without a change in statute. The FDA, as a former commissioner and associate commissioner have described, is a public health agency,⁸ but as an agency endowed with powers under our constitutional democratic republic, the FDA is first and foremost a public agency.

In this spirit, I focus here upon two recommendations, the second and the fourth.

cases is done in center-specific rule-writing teams, and these teams are often the target of *ex parte* contacts and implicit lobbying.¹¹

Rulemaking and guidance development would seem to be critically involved in the development of safe and effective medical products, and rulemaking is also where capture can happen.¹² Whether capture is occurring at the FDA is an open question. Capture is especially hard to detect and measure,¹³ and existing accounts suggest that historically, up until the 1990s, say, the FDA was likely not heavily captured by the industry it regulates. Yet a number of recent reports suggest that the situation may have changed in the last two decades.¹⁴

So while I generally laud the report, I think a truly meaningful approach to transparency of decision making at the FDA needs to go further, take a broader view, and to consider what the stakes of transparency really are. Doing so need not restrict anyone to moves that can be administratively implemented without a change in statute. The FDA, as a former commissioner and associate commissioner have described, is a public health agency,⁸ but as an agency endowed with powers under our constitutional democratic republic, the FDA is first and foremost a public agency.

“2. FDA Should Disclose More of Its Own Analysis and Decision-Making.”

The Working Group focuses on disclosure of data related to health, and in an important recommendation they call for more disclosure of the data on which the FDA makes its decisions. It is surprising, then, that no attention is given to rulemaking and guidance development, not least because recent research suggests that significant transparency issues prevail in this area.⁹

The Working Group might have believed, mistakenly, that the “development of safe and effective medical products” was something for which a focus on “specific” product approval decisions and not “general” guidances and rules was necessary. Yet both the longer and recent history of FDA decision making suggest that rulemaking and guidance development is never separable from case-specific clinical development and drug approval. One process informs the other, both ways, in real time. As the history of the Drug Efficacy Study Initiative (DESI) suggests, product approval decisions at the FDA operate in a common-law like fashion of aggregation in which particular patterns of decisions cumulate into guidances, which later become the basis for rules.¹⁰ The critical work in these

A robust transparency policy in rulemaking and guidance development would require the agency to disclose not merely the “data” that entered into its decision making but also the many sources of industry and other special interest influence, to disclose conflicts of interest among staff (their former careers) and advisers and consultants, and to disclose more fully communications between agency officials and between agency officials and industry officials and affiliated academics.

There have been some positive moves in this direction, as with the recent and controversial approval of eteplirsen (Sarepta) for Duchenne’s Muscular Dystrophy.¹⁵ Yet in a number of other cases, such as the agency’s badly bungled cost-benefit analysis of tobacco regulations (distinct in principle from pharmaceutical regulation but which involved a number of officials who also review rules on drugs),¹⁶ critical measures and policies of transparency were lacking. Did tobacco industry lobbyists or their allies influence the cost-benefit analysis of this rule? Did inappropriate ideological and non-scientific considerations enter the calculus? Have pharmaceutical industry lobbyists or interest-conflicted academics influenced rules or guidance documents, or have inappropriate ideologi-

cal commitments had influence there, too? There is nothing necessarily illegal about these possible patterns of influence, but the public has every right to know about them, and good public policy demands this kind of transparency, whether or not the interests of “safe and effective development of medical products” are served.

4. FDA Should Correct Misleading Information in the Market

Among the most useful proposals of the Working Group is that the FDA should do more than disclose information. The agency should actively determine which information about drugs is misleading, the Working Group proposes, and counter that false information not merely by disclosing but effectively by publicizing information of its own. In ways that echo Jerry Avorn’s brilliant strategy of counter-marketing — also known as “academic detailing”¹⁷ — the Working Group calls for an affirmative strategy of openly correcting misleading information by dint of the FDA releasing its own, countervailing information.

Let’s be clear that this is far more than a transparency policy. In order to be effective, it will have to be a publicity policy, and to the extent it is at all effective it will be greeted with hostility by some of the medical products industry’s most ardent defenders in the interest group domain, at think tanks and universities, and among politicians. The moment that FDA “disclosure policy” becomes a competitor and a counterweight to pharmaceutical company advertising and marketing, we can at least imagine, if not wager, that industry-aligned politicians will be involved in trying to restrict what the agency can do, by outlawing such disclosure or by gutting the budget for such activities.

So the Working Group should be aware, if it is not already, that this particular recommendation will succeed or fail not on the battlefield of policy experimentation and cost-effectiveness, but that of raw industrial and indeed partisan politics. Yet I support the recommendation, not least because given the state of First Amendment litigation restricting the agency’s ability to constrain off-label marketing and claims, FDA statements to correct misleading information may be the best way to provide the public with product-neutral information to rebut misleading claims. Such information amounts to a form a “public good” not merely in the literal sense of the term but also in its economic meaning, in the sense that incentives for its provision are weak and attenuated.

Some of the work here can be done by extending the report’s other suggestions. If, for instance, the FDA continues to publish clinical trial data from failed trials — which recent research suggests are poorly sup-

plied¹⁸ — then some of the work of countering misleading information will occur, at least in the sense of pure disclosure. Yet in an oversaturated world of information, there has to be more to effective disclosure policy and practice than creating an unpublicized website that no one visits.

Conclusion: From Disclosure to Publicity

The Working Group has produced a valuable document. To the extent that it succeeds, however, it will have to tackle questions of politics in at least two ways.

The first, as I have indicated, is that there is industrial influence in the very operation of the FDA (not merely “disagreements” as the Working Group notes on page 5 (note 4)), and a public-regarding transparency policy that coheres with the academic literature on the subject cannot ignore this imperative. An entire academic literature has recognized that transparency in government administration means more than disclosure of data. There are public interests far beyond safe and effective medical products involved.

Second, successful disclosure of agency information will need to ensure that it actually reaches the public, cognizant of the fact that there are competing information channels at work that spend billions of dollars a year getting their own messages out. Data that is merely “disclosed” is likely not to be used. The medical products industry, to be sure, does far more than “disclose” data favorable to its products — it places those who know this data (marketers, detailers and representatives, as well as academic allies) in doctor’s offices, in operating rooms, at professional conferences, in all or most of the very places where human attention and memory processes are most likely to result in its absorption and retention. It spends billions of dollars repeating these messages on television, in print and on the Internet and social media. That is entirely appropriate and legal, but the public interest will certainly be ill served if special-interest information favorable to products is subsidized while public-interest information neutral among products is not.

One might reply that transparency policy should be focused on what the FDA chooses to make public somehow, somewhere — “getting it out there” — without inappropriate attention to how that information is distributed. Yet this alternative, if pursued alone, risks a deep and abiding naïveté. The FDA could in theory adopt the entirety of the Working Group’s recommendations and yet simply place some links on a website, combined with one-time announcements of its availability. The imbalance of messaging would result in the data being drowned out by other, competing and potentially misleading claims. The First Amendment may currently prevent the FDA from prohibiting cer-

tain claims about products, but in no way does it prevent the FDA from making strong, evidence-based and widely publicized claims that counter the companies' misleading statements and marketing.

Effective transparency in an inescapably political world, then, requires distribution of the relevant information. Absent what amounts to a real advertising and marketing budget, even a robust transparency policy in the sense envisioned by the Working Group is likely to fail.

Note

The author has no conflict of interest to declare.

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Clinical Trial Transparency: The FDA Should and Can Do More

Amy Kapczynski and Jeanie Kim

In recent years, the scientific community and regulators have increasingly recognized the value of data transparency in clinical research. Adding to this momentum, the *Blueprint for Transparency at the FDA* calls upon the U.S. Food and Drug Administration to act as a key intermediary for sharing clinical trial data. We strongly support the *Blueprint's* recommendations for the FDA to proactively release substantially more pre-market and post-market clinical trial data submitted by companies. The FDA is in a particularly good position to facilitate public disclosure of data. Tasked with comprehensively regulating the drugs, devices, and biologics on the U.S. market, the agency has access to a wealth of clinical trial data and receives more data than its European counterpart.¹ Notably, the recently appointed FDA Commissioner Scott Gottlieb has expressed his support for data transparency, acknowledging that the agency should leverage its regulatory authority to release data in the public's interest.²

In this brief commentary, we show that the FDA has the legal authority to share much more clinical trial data that it currently does. We also show that the primary existing route for obtaining such data from the FDA — individual requests under the Freedom

of Information Act (FOIA) — can be used to obtain important categories of data, particularly summary data and metadata. But FOIA cannot substitute for a comprehensive data sharing system that prioritizes public health. The FOIA approach can take years, often requires litigation, and will be piecemeal and reactive in nature. A more proactive approach to the release of data would allow the FDA to set priorities and to build a platform for data sharing that maximizes the benefits for patients and the research community. Such a platform could also, when appropriate, craft data use agreements that protect patient privacy while promoting research integrity and transparency.

The FDA Should Proactively Share More Clinical Trial Data

The FDA's core public health mission is to ensure that medicines are safe and effective for their intended uses — a task primarily accomplished by evaluating the rigor and sufficiency of the evidence submitted by companies. By sharing data from clinical studies, the FDA can improve the evidence base that informs patients, providers, and payers, and help protect the integrity of the clinical research enterprise. In 2015, the Institute of Medicine (IoM) released one of the most comprehensive reports in support of sharing data from clinical trials.³ The report defines three categories of clinical trial data: "individual participant data" (i.e., raw data and the analyzable data set); metadata, or 'data about the data' (e.g., protocol, statistical analysis plan, and analytic code); and summary-level data (e.g., summary-level results posted on registries, lay summaries, publications, and [clinical study reports (CSRs) submitted for regulatory review]).⁴

As the report emphasizes, transparency for each category offers distinct benefits. By sharing summary

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results, the FDA can “help[] protect against publication bias.”⁵ Many clinical trial results that are submitted for regulatory review are unpublished or differ significantly from the results that are selectively reported in journals.⁶ Disseminating summary data ensures that patients and the research community have access to all trial results that are relevant for clinical care, and not just the positive or favorable outcomes.⁷ Furthermore, the FDA receives detailed summaries in CSRs that contain far more information than what is found in publications.⁸ Making CSRs publicly available “allows for better understanding of regulatory decisions and facilitates the use of analyzable data set.”⁹ Clinical trial protocols should also be shared because they provide context for understanding published data, as well as any summary data and analyzable data that are shared.¹⁰

The FDA is reportedly the only regulator that routinely obtains analyzable data sets.¹¹ The sharing of such data sets, accompanied by study protocols and summary data, to qualified independent researchers “allows for reanalysis, meta-analysis, and scientific discovery through hypothesis generation.”¹² Secondary researchers can help identify issues that may have been missed by regulators or understudied or buried by companies.¹³

The FDA Can Proactively Share More Clinical Trial Data

Despite the potential benefits, the FDA does not proactively share most of the clinical trial data in its possession in any comprehensive fashion. Congress has set forth baseline disclosure requirements for the FDA as well as some confidentiality obligations. However, much of the data submitted to the FDA falls somewhere between these two poles, giving the FDA discretion to determine what should be made available in the public’s interest and what should be kept confidential.

Federal agencies generally have the authority to release information to the public if the release is not otherwise forbidden by law. FOIA, enacted in 1966, embodies this core presumption in favor of transparency.¹⁴ In passing FOIA, Congress evinced “a general philosophy of full agency disclosure unless information is exempted under clearly delineated statutory language.”¹⁵ Moreover, while FOIA provides several exemptions, including Exemption 4 for “confidential commercial information” (CCI) and Exemption 6 for personal privacy,¹⁶ courts have found that Congress did not intend for the exemptions themselves to create absolute bars to disclosure.¹⁷ Rather, the exemptions are “workable standards” designed to *permit* an agency to withhold certain information without limiting its discretion to disclose that information either proactively or in response to a FOIA request.¹⁸

In general, even if information falls under an exemption, agencies have the discretion to release it if there is a compelling public interest in disclosure related to the agency’s activities and and if the disclosure is not barred by another law.¹⁹

The FDA has yet to fully exert its discretion to release much of the summary data, metadata, and individual participant data (IPD) in its possession. To do so, the FDA would first have to recognize that many types of clinical trial data can be shared without genuine risks to patient privacy. Summary-level trial results, CSRs, and study protocols typically contain no patient-specific information or can be easily redacted to remove patient identifiers.²⁰ Analyzable data sets present more complex privacy concerns, and some may be difficult to fully de-identify without rendering them useless for secondary analyses.²¹ However, emerging protocols for de-identification make it possible to sufficiently anonymize certain analyzable IPD so that the risk of re-identification is very small.²² Agencies have the discretion to weigh legitimate personal privacy concerns against the public interest in disclosure and to share data if the privacy risks are minimal in relation to a public benefit.²³ The FDA is well positioned to consider the privacy risks and public health benefits associated with sharing different types of clinical trial data, and the FDA and the U.S. Department of Health and Human Services have both signaled interest in exploring ways to share de-identified IPD from clinical trials submitted for regulatory review.²⁴

While agencies have less discretion with respect to CCI because of overlapping nondisclosure laws that prohibit federal employees from unauthorized release of commercial or financial data, they are still entitled to substantial deference to determine the initial threshold question of what constitutes CCI.²⁵ This is a critical point for the FDA when considering various types of clinical trial data. Much of the clinical trial data that researchers need for meta-analyses and secondary analyses simply is not CCI, or can be redacted to address any CCI concerns. The IoM Report describes how commercially sensitive information that reflects a company’s business strategies and clinical development processes can be separated from analyzable data that are more objectively collected and tabulated.²⁶ For example, CSRs, which contain manufacturing formulas or clinical trial site information, can be redacted to address legitimate CCI issues. Courts have also rejected CCI arguments for certain types of clinical research data, including postmarket study protocols and raw safety data, where the claims of competitive harm are negligible or vague.²⁷

The FDA’s lack of proactive disclosure is particularly problematic where data relevant to drug safety

is concerned, because Congress has expressed in clear terms its intention that the agency disclose data relevant to that question. The Food and Drug Administration and Amendments Act (FDAAA) instructs the FDA to maintain a website that provides patients and providers with better access to safety information about drugs and biologics.²⁸ The FDA must post the most recent FDA-issued safety alerts, warning letters, links to the trial registry and results, and “*other material* determined appropriate by the [agency].”²⁹ To fulfill its obligation to release “other material” pertinent to patient safety, the FDA should routinely release at least data like CSRs, summary results, full protocols, and analyzable datasets that can be de-identified.³⁰ These data are pertinent to drug safety, and to the bal-

particularly Exemptions 4 and 6, and affirm the scientific and public health value of data sharing. This is particularly appropriate where, as in the case of data that sheds light on drug safety, Congress has expressed its view that an interest is especially compelling.

Leveraging FOIA to Obtain Clinical Trial Data from FDA: A Partial Solution

When faced with requests for particular clinical trial data, the FDA has in fact released many types of clinical trial data, implicitly conceding that such disclosures do not raise commercial confidentiality or personal privacy concerns. We recently used FOIA to seek access to clinical trial data for Gilead’s blockbuster Hepatitis C drugs, sofosbuvir (Sovaldi) and ledipas-

Until the FDA proactively releases data on a routine basis, individual FOIA requests are the only mechanism to obtain data that the agency does not release. Our experience with FOIA shows that the process can be a very powerful tool for obtaining clinical trial data, at least of the summary and metadata variety, but that FOIA also has important limits. First, valid FOIA requests can go unfulfilled without the aid of a lawyer to take the agency to court for its failure to timely respond. Second, even when successful, the process is slow. Requests for clinical trial data are likely to be put in the slower “complex” queue because of the high volume and complexity of the data as well as the need for redactions, and so typically it will take years to resolve.

ancing of risks against clinical benefits for particular indications, and can help patients, providers, and the research community fully understand the safety profile of drugs and devices.

Congress has also pressed the FDA to be more forthcoming and has urged the agency to incorporate broader transparency policies for the benefit of the public. Congress has done this not only in congressional hearings,³¹ but also through specific laws, such as statutory provisions that mandate the release of “action packages” — the FDA’s summaries of all safety and effectiveness data in its possession — for every approved new drug or biologic.³² These disclosure requirements are intended to address the discrepancies between the comprehensive information that the FDA possesses and the selective information that is publicly available, which in many cases have led to widespread patient harms.³³ In order to further bridge information gaps and increase the value of clinical research data, the FDA should revisit whether various types of data legitimately fall under FOIA exemptions,

vir/sofosbuvir (Harvoni).³⁴ Although it took two years of litigation, the FDA has now released tens of thousands of pages of summary data and metadata, including safety and effectiveness summary-level data, full protocols that include analysis plans and amendments, and CSRs. The agency redacted very little — for example, select information about ingredients and manufacturing information that was commercially confidential, and participant contact information that implicated privacy. Notably, Gilead had intervened in the case early on, thereby presumably consenting to all data disclosures and implicitly admitting that there are few CCI and privacy concerns relevant to these categories of data, and that those that exist can be addressed through simple redactions.

Our suit did not resolve the extent to which FOIA can be used to access IPD and analyzable datasets. The orientation of FOIA — a disclosure law designed for all types of governmental information — may sometimes make it a blunt tool for these purposes. FOIA rests on a philosophy of broad public dissemination and equal

access to information. Once one entity receives information under FOIA, the public as a whole is presumed to have the right to access the same material.³⁵ Courts have historically found that selective or conditional data disclosure arrangements are not consistent with the purpose of FOIA.³⁶ However, such arrangements — like data use agreements with confidentiality provisions — may, depending on the circumstances, be the best means of sharing analyzable data to secondary researchers at a reasonable cost, while also protecting patient privacy and commercial interests.³⁷

Until the FDA proactively releases data on a routine basis, individual FOIA requests are the only mechanism to obtain data that the agency does not release. Our experience with FOIA shows that the process can be a very powerful tool for obtaining clinical trial data, at least of the summary and metadata variety, but that FOIA also has important limits. First, valid FOIA requests can go unfulfilled without the aid of a lawyer to take the agency to court for its failure to timely respond. Second, even when successful, the process is slow. Requests for clinical trial data are likely to be put in the slower “complex” queue because of the high volume and complexity of the data as well as the need for redactions, and so typically it will take years to resolve.³⁸ Despite the hundreds of hours of legal assistance, it took us nearly two years to begin receiving data pursuant to our FOIA request.³⁹ The process can be slow even where a research question is exceptionally urgent, and the FDA grants “expedited processing.” In 2014 and 2015, the FDA completed two requests that were granted expedited processing; it took the agency 693 days and 862 days respectively to finish document production.⁴⁰

FOIA is also better suited to individual requests for specific data than for systematic release of data of scientific and public health importance. Production of data generally occurs piecemeal for practical reasons, and recipients of data may, but are not obliged to, release the data they receive to others. Proactive release of data by the FDA would be preferable to the current reactive approach for many reasons. It would allow the agency to ensure that researchers have equitable access to data. The agency could also — and should — prioritize, releasing first those categories of information that are both important and readily redactable, such as CSRs and protocols for widely prescribed drugs. Proactive release would also allow the agency — possibly with additional appropriations — to create a dedicated and centralized platform, alone or in conjunction with other entities, that would give investigators with legitimate scientific and public health inquiries access to redacted and de-identified datasets, similar to the National Institutes of Health’s

database for biomedical and clinical research.⁴¹ The FDA could also design optimal conditions for data sharing. For an example, where appropriate, the agency could implement data use agreements that prohibit improper uses of shared data or further promote transparency by requiring that results of studies using the data be publicly shared.⁴²

By proactively sharing data, the FDA can address the limitations of FOIA and create data sharing policies that promote the health and safety of all Americans. The public interest in data disclosure is more urgent and compelling now than when the FDA first formulated its disclosure policies. With modern advances in data generation and analyses, there is an even greater potential for data sharing to enhance and accelerate medical knowledge. By proactively sharing data, the FDA can better fulfill its responsibilities to patients and public health.

Note

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4. *Id.*, at 7 (emphasis added).
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9. IoM Report, *supra* note 1, at 111.
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16. 5 U.S.C. § 552(b)(4) & (b)(6).
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18. *Chrysler Corp.*, 441 U.S. at 294 (quoting H. R.Rep. No. 1497, 89th Cong., 2d Sess., 2, 5 (1966)); see also *Dep’t of the Air Force v. Rose*, 425 U.S. at 361 (The FOIA exemptions “do not obscure the basic policy that disclosure, not secrecy, is the dominant objective of the Act,” and thus, they must be “narrowly construed”).
19. *CNA Fin. Corp. v. Donovan*, 830 F.2d 1132, 1134 n.1 (D.C. Cir. 1987) (“The agency’s decision to release the data normally will be grounded either in its view that none of the FOIA exemptions applies, and thus that disclosure is mandatory, or in its belief that release is justified in the exercise of its discretion, even though the data fall within one or more of the statutory exemptions.”); see *Jurewicz v. U.S. Dep’t of Agriculture*, 741 F.3d 1326, 1332 (D.C. Cir. 2014) (finding that a substantial privacy interest “must be balanced against any public interest in disclosure ... [to the extent that] disclosure of the information sought would ... let citizens know ‘what their government is up to.’” (quoting *U.S. Dep’t of Def. v. Fed. Labor Relations Auth.*, 510 U.S. 487, 497 (1994)). Where CCI is concerned, however, the balancing of public interests may be inappropriate because the category overlaps with other laws that flatly forbid agencies from making unauthorized disclosures of commercial data. *CNA Fin. Corp. v. Donovan*, 830 F.2d 1132, 1140 (D.C. Cir. 1987) (finding that 18 U.S.C. § 1905 “appears to cover practically any commercial or financial data collected by any federal employee” such that information that falls under Exemption 4 is barred from disclosure unless otherwise authorized). But, the U.S. Court of Appeals for the Seventh Circuit has suggested a different interpretation — that § 1905 was intended to protect a narrower category of information than Exemption 4, thereby preserving some agency discretion to disclose information that falls within Exemption 4. *Gen. Elec. Co. v. U.S. Nuclear Regulatory Comm’n*, 750 F.2d 1394, 1402 (7th Cir. 1984) (“Exemption 4 is broadly worded, and it is hard to believe that Congress wanted seekers after information to stub their toes on a rather obscure criminal statute almost certainly designed to protect that narrower category of trade secrets ... whose disclosure could be devastating to the owners and not just harmful”).
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23. *U.S. Dep’t of the Air Force v. Rose*, 425 U.S. at 372 (finding that Exemption 6 requires a balancing of the individual’s right to privacy against the public’s right to disclosure under FOIA); *Consumers’ Checkbook Ctr. for the Study of Servs. v. U.S. Dep’t of Health and Human Servs.*, 554 F.3d 1046, 1057 (D.C. Cir. 2009) (stating that FOIA’s “presumption favoring disclosure ... is at its zenith under Exemption 6”) (quoting *Nat’l Ass’n of Home Builders v. Norton*, 309 F.3d 26, 37 (D.C. Cir. 2002)); see also *Jurewicz v. U.S. Dep’t of Agriculture*, 741 F.3d 1326, 1331-34 (D.C. Cir. 2014) (in reverse-FOIA case, deferring to an agency’s decision that that any personal privacy concerns are minimum and outweighed by the public’s interest “in assessing whether the [agency] is fulfilling its statutory mandate” and “gaug[ing] the effectiveness of [agency] inspections by comparing data ... with publicly available inspection reports”).
24. In 2013, the FDA proposed sharing de-identified analyzable safety and efficacy datasets, acknowledging that such data “have tremendous potential to ... provide new opportunities for innovation in medical product development.” “Availability of Masked & Deidentified Non-Summary Safety & Efficacy; Request for Comments,” 78 *Federal Register* 33421, 33422 (June 3, 2013). More recently, in 2016, the U.S. Department of Health and Human Services has expressed a willingness to explore whether *ClinicalTrials.gov* can “provide[] the scaffolding on which individual participant data ... (the next frontier in transparency) and other trial “meta-data” can be organized in the future,” and the agency “anticipate[s] that *ClinicalTrials.gov* can be used in the future to catalyze IPD sharing.” “Clinical Trials Registration and Results Submission Final Rule,” 81 *Federal Register* 64,981, 64,988, 64,991 (Sept. 21, 2016) (codified at 42 C.F.R. Pt. 11).
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26. IoM Report, *supra* note 1, at 259-60.
27. *Pub. Citizen Health Research Group v. U.S. Food and Drug Admin.*, 964 F. Supp. 413 (D.D.C. 1997) (ordering release of post-market study protocols after finding that disclosure would not result in competitive harm); *Pub. Citizen Health Research Group v. U.S. Food and Drug Admin.*, 2000 WL 34262802 (D.D.C. 2000) (holding that CCI claims were vague and ordered release of underlying raw data to a graph with safety information given to an advisory committee); see also *Teich v. U.S. Food and Drug Admin.*, 751 F. Supp. 243, 255 (D.D.C. 1990) (rejecting FDA’s argument that the requested animal studies and consumer complaints are CCI and found that any competitive harm is “negligible”).
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29. 21 U.S.C. § 355(r)(2)(B) (emphasis added).
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32. 21 U.S.C. § 355(l)(2); FDAAA § 916.
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- State of New York v. GlaxoSmithKline*, 401707/2004 (N.Y. Sup. Ct. June 2, 2004), available at <<http://news.findlaw.com/wsj/docs/glaxo/nyagglaxo60204cmp.pdf>> (last visited November 2, 2017).
34. *Treatment Action Group et al v. U.S. Food & Drug Admin.*, No. 15-cv-976 (VAB) (D. Conn. Sept. 20, 2016).
35. 5 U.S.C. § 552(a)(3) (all records requested under FOIA that are not exempt must be made “promptly available to any person”); *Dep’t of Justice v. Reporters Comm. for Freedom of Press*, 489 U.S. 749, 771 (1989) (FOIA is “clearly intended ... to give any member of the public as much right to disclosure as one with a special interest”) (quoting *NLRB v. Sears, Roebuck & Co.*, 421 U.S. 132, 149 (1975)).
36. See *Swan v. SEC*, 96 F.3d 498, 500 (D.C. Cir. 1996) (“Once records are released, nothing in FOIA prevents the requester from disclosing the information to anyone else. The statute contains no provisions requiring confidentiality agreements or similar conditions.”); *Maricopa Audubon Soc. v. U.S. Forest Serv.*, 108 F.3d 1082, 1088–89 (9th Cir. 1997) (holding “that FOIA does not permit selective disclosure of information only to certain parties, and that once the information is disclosed . . . it must also be made available to all members of the public who request it.”)
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FDA and the Marketplace of Ideas for Medical Products

Nathan Cortez

Modern free speech law is predicated on an analogy. Just as superior products and services will prevail in a free and open market, so too superior ideas (and ideally, the truth) will prevail in a free and open “marketplace of ideas.”¹ Inspired by laissez-faire economics, the analogy suggests that free expression, with minimal government interference, will generate the best ideas and the most truth.²

But consider the marketplace of ideas for medical products, specifically those under premarket review by the U.S. Food and Drug Administration (FDA). There is significant demand for information about such products. Investors and patient groups often keep close track of announcements concerning investigational products, including clinical trial findings and milestones in the FDA review process.³ But competitive pressures on companies and publication pressures on researchers often result in selective publication of study results, whereby positive findings are published and publicized, while negative ones are not.⁴ Considering the immense financial stakes of FDA approval, companies sometimes exaggerate or embellish study results or the product’s review status with the FDA. Thus, the “marketplace of ideas” for investigational products can present a highly skewed picture of the product, particularly its likely benefits and risks — a “market failure,” to follow the analogy.

Should the FDA more actively correct such market failures? Should the agency correct misleading information released about products in development? This question, among others, is taken up by the FDA Transparency Working Group, whose Blueprint points to

two recent examples.⁵ In 2013, the company Sarepta publicized study results for a drug being developed to treat Duchenne muscular dystrophy, but excluded from the analysis two patients with adverse outcomes, despite objections to such post-hoc calculations by the lead reviewer for the FDA’s Advisory Committee.⁶ Then, in March 2015, the company Orexigen filed a report with the Securities and Exchange Commission (SEC) that misstated unpublished evidence regarding the potential cardiovascular benefits of a drug being studied for obesity, despite the FDA’s contrary view.⁷ In neither case did the FDA counter the misleading statements or correct the “failure” in the marketplace of information.⁸

Of course, the marketplace of information for investigational products is not a completely free and unfettered one — and for good reason. Before the FDA has reviewed the scientific basis and clinical evidence supporting a product’s intended uses, it is premature to make claims regarding its safety and effectiveness. Thus, the FDA carefully restricts promotion for investigational products, but allows “the full exchange of scientific information concerning the drug, including dissemination of scientific findings in scientific or lay media.”⁹ Of course, drawing the line between promotional and scientific exchange can be difficult.

For example, the FDA has long been reluctant to interfere with mandatory disclosures required by securities laws.¹⁰ The agency has explained that its rules do not bar disclosing study results in SEC reports or press releases to investors, so long as the communication makes no claims regarding safety or efficacy and does not otherwise commercialize the product prior to approval.¹¹ Ordinarily, the FDA will not object to information required by the SEC, but will scrutinize statements that are gratuitous or embellished.¹² So, for

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example, the FDA does not object when companies make non-promotional announcements required by the SEC regarding their research activities or products in development, but may object to information that tries to characterize safety or efficacy data or otherwise makes claims about intended uses.

Over time, the FDA has grown skeptical of companies invoking their SEC obligations in response to FDA objections.¹³ FDA officials see a lack of symmetry, as companies are quick to publicize favorable study results or FDA approvals, but are exceedingly discreet (or even silent) regarding negative events that should be equally “material” to investors under securities laws.¹⁴ Perhaps worse is when a company with no publicly-traded securities invokes the “SEC defense.”¹⁵ Thus, the FDA and SEC have formal mechanisms for sharing information and expertise on corporate disclosures for FDA-regulated products.¹⁶ In some instances, the SEC has even suspended public trading for a company’s stock after the company made misleading statements about clinical trial results or a product’s FDA approval status,¹⁷ perhaps reflecting increased scrutiny after the ImClone scandal.¹⁸

But enforcement actions like these can take years before misinformation is corrected. So when, and how, should the FDA correct misleading statements? Current FDA regulations give the Commissioner discretion to disclose all or part of any FDA record when in the “public interest,” when consistent with privacy, property, and trade secret rights, and when consistent with the agency’s need to promote frank internal deliberations.²² But FDA rarely invokes this discretion.²³ Moreover, the rule exempts from disclosure trade secrets and other confidential commercial information.²⁴

The Blueprint thus recommends that the FDA more actively correct misleading information released about products in development, noting that such information can mislead physicians, patients, investors, and other audiences when not corrected.²⁵ Corrections are justified, according to the Blueprint, when “the information has the potential to cause significant confusion in the medical community and among patients,” or when it is “vital to public health.”²⁶ This recommendation largely mirrors the 2010 FDA Transparency Initiative Task Force’s recommendation that summary

The FDA should publish guidelines detailing when and how the agency will correct misleading information for investigational products, allowing the agency to counterbalance the overwhelming financial incentives companies often have to exaggerate or embellish. Such guidelines would signal to companies that quick corrections to the marketplace of information would be possible. The guidelines would also be particularly important given flexible new approval standards introduced in the 21st Century Cures Act.

Nevertheless, abuses remain, forcing courts and agencies to police the marketplace of information. In 2013, the 9th Circuit Court of Appeals upheld the fraud conviction of Scott Harkonen, a drug company’s former senior director of biostatistics, who had issued a press release misrepresenting clinical trial results for interferon gamma-1b (Actimmune). The court held that fraudulent commercial speech is entitled to no First Amendment protection.¹⁹ And in 2016, AVEO Pharmaceuticals paid a \$4 million penalty to settle SEC charges that the company failed to disclose the FDA’s safety concerns with a drug under review, including FDA staff recommendations that the company conduct an additional clinical trial.²⁰ The SEC also pursued charges against three former officers of AVEO, including its former CEO, chief financial officer, and chief medical officer.²¹

safety and efficacy information be released when “in the interest of public health,” including when “necessary to correct misleading information.”²⁷

In rare instances the FDA has taken to heart a recommendation by courts that the preferred remedy for potentially false or misleading speech is “more disclosure, rather than less,”²⁸ issuing the agency’s own publicity to counter publicity by companies that the FDA found objectionable.²⁹ But given complaints about the fairness of this method, including the lack of advanced notice,³⁰ the FDA does not invoke this remedy often.

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corrections to the marketplace of information would be possible. The guidelines would also be particularly important given flexible new approval standards introduced in the 21st Century Cures Act. The Cures Act directs the FDA to consider “real world evidence” when considering new uses for approved drugs, relaxing the agency’s longtime insistence on randomized clinical trials.³¹ Such “real world evidence” may be more likely to be mischaracterized by manufacturers and misunderstood by the public. The Blueprint thus can be an important counterweight not only to existing problems, but also to problems generated by the Cures Act.

Note

The author has no conflict of interest to declare.

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2. S. Ingber, “The Marketplace of Ideas: A Legitimizing Myth,” 1984 *Duke Law Journal* 1 (1984): 5. In *Sorrell v. IMS Health*, 564 U.S. 552, 583 (2011), Justice Breyer’s dissent invokes the “marketplace of ideas” analogy, citing Justice Holmes’ dissent in *Abrams v. United States*, *supra*. However, Breyer notes that for commercial speech, information about goods and services is rightly regulated, and that such regulation is subject to intermediate rather than strict scrutiny.
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21. *Id.*
22. 21 C.F.R. § 20.82.
23. Blueprint, *supra* note 5, at 29.
24. 21 C.F.R. § 20.82(b)(1).
25. Blueprint, *supra* note 5, at 28-29.
26. *Id.*, at 30.
27. *FDA Transparency Initiative: Draft Proposals for Public Comment Regarding Disclosure Policies of the U.S. Food and Drug Administration* (May 2010), at 48-49 (Draft Proposal 16).
28. *Pearson v. Shalala*, 164 F.3d 650, 657 (D.C. Cir. 1999).
29. See, e.g., FDA, *Talk Paper T03-18: FDA Warns Public about Misrepresentations in Marketing Claims About Drug to Treat Cancer* (Mar. 14, 2003).
30. See N. Cortez, “Adverse Publicity by Administrative Agencies in the Internet Era,” *BYU Law Review* 2001, no. 5 (2011): 1371-1454. Note that the Blueprint recommends giving the company advanced notice, but also calls for the FDA to be able to “move quickly to protect patients in response to urgent public health needs,” Blueprint, *supra* note 5, at 30, echoing earlier recommendations. Cortez, *Adverse Publicity*, at 1437.
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Disclose Data Publicly, without Restriction

Peter Doshi and Tom Jefferson

The FDA holds more clinical trial data than any other body on the planet, more than any other regulator and more than any single pharmaceutical company. And at present the FDA sits on those data, treating such data as commercial confidential information that it is not at liberty to disclose.¹ This prevents systematic reviewers, guideline committees, other public health bodies, and other third parties from independent evaluation of the clinical evidence the FDA relied upon to determine the benefits and harms of medicines. In other words, ‘no sunlight please — we know what is best for you.’ This must end, and the Blueprint rightly calls on FDA to “disclose data from scientific studies to enhance understanding of medical products.”²

Since concerns about publication bias emerged decades ago,³ systematic reviewers have paid particular attention to addressing the vexing problem of unpublished trials.⁴ But over the past decade, additional grave concerns have emerged over the trustworthiness of even those clinical trials that are published.⁵ The inescapable conclusion from this growing body of research is that what we see, even in the most highly regarded peer-reviewed journals, cannot be trusted at face value. We know this only for selected cases, such as with the drugs rofecoxib, celecoxib, paroxetine, gabapentin, and oseltamivir, and often only because litigation or public pressure helped force company reports

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of clinical trials into the public domain: “clinical study reports.” These are unabridged reports of clinical studies created by industry following a set format primarily for regulatory review.⁶ Publications by contrast may omit or minimize mention of serious adverse events that occurred during the trial. They may misreport the trial’s primary endpoint, the duration of the trial, or other aspects of the protocol. They may fail to disclose limitations in reliability of the collected data, or lapses in the conduct of the trial. They may describe a substance as placebo when it’s not inert or they may fragment a dataset in a number of reports — some visible, some not.

Those that believe sound clinical decisions can be made based on the evidence available in journal publications alone are, whether they realize it or not, betting that the problems that have been discovered thus far are “in the past,” “bad apples,” “all fixed” and that under reporting and mis-reporting of trials no longer occurs. This is a dangerous and costly bet to make on human welfare. It also is an unnecessary bet, as the raw data from clinical trials already exists. All it takes is disclosure of the data to enable independent scrutiny.

We therefore believe that public disclosure of the clinical trial data in FDA’s possession is not simply an “opportunity to enhance transparency at FDA,” to quote the Blueprint, but is rather an ethical imperative to ensure evidence-based medicine is truly based on evidence and not a selected summary of it.

Public Release or Not?

Now comes the issue of just how to disclose clinical study reports (Recommendation 16). In this regard, we believe the Blueprint’s suggestions need clarifying. The Blueprint advocates both “harmonizing FDA

policy with that of the European Medicines Agency” (which has been releasing clinical study reports since late 2010 through a freedom of information-like mechanism) and using a repository that “employ[s] safeguards” prior to sharing individual participant data, including verifying that “the research proposed would advance science or improve public health and healthcare, check institutional status, and create legally enforceable agreements that ensure applicants will not compromise patient identity.” These suggestions must be considered in light of the fact that the EMA does not screen requests, a fundamental and important contrast to the many data access (not data sharing) systems now available such as the joint pharmaceutical company sponsored ClinicalStudyDataRequest.com. While we share the aims of groups making data accessible — ensuring responsible research conduct, protecting the rights of patients, and good data stewardship — we disagree that gatekeeping is

vacy and integrity of individuals that may be named — or discoverable — in documents.⁹ A second policy the EMA launched last year (policy 0070) proactively publishes clinical study reports to the web.¹⁰

Individual Participant Data

While clinical study reports are paper (PDF) documents that routinely run hundreds to thousands of pages in length, electronic patient level datasets raise heightened concerns about the risk of re-identification of patients. There is no doubt that this risk increases with access to electronic patient level datasets. Even if patients cannot be re-identified using a single trial dataset, risk of re-identification rises with linkage to other datasets. As EMA does not routinely request participant level data, whereas the FDA does, FDA must forge new ground in setting standards of how to effectively balance the imperative to share these data while also working to reduce the risk of re-identifi-

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the appropriate means to that end and we have several years’ experience to back our views. We place more faith in the structures of open science to police misconduct and reward good behavior, and believe a regulator’s duty in a political democracy is to ensure the basis for all citizens to make informed decisions about medicines based on the data in its possession. Thus we challenge the Blueprint’s proposed scope for limiting FDA’s transparency involvement in this area to only those trials “where sponsors have not already made their data available by other means.” Researchers who have reused data from ClinicalStudyDataRequest.com have called it like doing research “through a periscope”;⁷ this is unsatisfactory.

The gatekeeper-free approach EMA adopted is thus the correct one, but it suffers from an inability to keep pace with the volume of requests. In 2013, the agency received less than 300 requests through its “reactive” access to documents policy 0043. In 2016, it received more than 800, and by the end of 2017, these are likely to top 1000.⁸ Overload has set in despite an increase in staff to 12 full-time employees that communicate with requestors and sponsors of affected products and oversee the redaction process to protect the pri-

vation of participants. Because the probability of re-identification, even after anonymization, is generally not zero, the pros and cons of various control mechanisms (such as contracts or more restrictive terms on access) will need to be considered. Public release of data, without restriction, may pose a low risk of re-identification for certain clinical trial datasets whereas for other datasets, more restrictive measures may be necessary to meet the public’s perception of “acceptable risk.” This is a field that data scientists have been working in for some time, and the FDA should elicit their contribution in establishing standards.¹¹

Correcting Misleading Information

In the few years that have now passed since the launch of EMA Policy 0043, YODA, and ClinicalStudyDataRequest.com, one can ask whether these systems for data sharing and data access-without-sharing are being sufficiently used with outcomes that offset the cost and effort involved in making them exist. We think the answer is a definite ‘yes’ and as evidence offer the case of oseltamivir. Since 2004, the US government in the pandemic influenza preparedness and response plan offered a scientific rationale to justify

its stockpiling of influenza: the drug was to cut rates of serious complications of influenza and hospitalizations in half.¹² This rationale was based on a six-page journal article; four of the six authors were employees of the manufacturer, and one was a paid consultant.¹³

Had our Cochrane review team reviewed clinical study reports in the year 2000 rather than 2011, we could have shown that oseltamivir was not proven to reduce these risks years before governments stockpiled billions of dollars worth of the drug.¹⁴ Just one oseltamivir-like experience every decade surely offers the opportunity to correct misleading information and save orders of magnitude more money than it costs to ensure timely public access to clinical trial data in FDA's possession.

At the same time, FDA is in a position to do more than just release clinical trial data. It can also help "correct misleading information in the market" itself, as the Blueprint advocates (Recommendation 15). In numerous cases, important discrepancies between the published reports of clinical trials and the data submitted to FDA are known to FDA scientists. Quickly correcting misleading publications of trials soon after drug approval could prevent many adverse downstream effects, and FDA scientists are well positioned to do this.¹⁵ If all it takes to achieve this aim are extra resources, then we think these would be well spent, considering the threat to life and tax payers' wallets that the cited cases entailed. We therefore believe that in addition to the Blueprint's prudent suggestions to establish a standard for correcting misleading information by public servants, the Agency should also actively encourage its scientists to help ensure the accuracy of the medical literature by engaging directly, without need for sign-off from one's superiors. Less bureaucracy and secrecy and more sunlight is needed if regulation is to regain its lost reputation and fulfill its public health mission.

Note

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In addition, Dr. Jefferson receives royalties from his books published by Blackwells and Il Pensiero Scientifico Editore, Rome. Dr. Jefferson is occasionally interviewed by market research companies for anonymous interviews about Phase 1 or 2 pharmaceutical products. In 2011-2013, Dr. Jefferson acted as an expert witness in a litigation case related to oseltamivir phosphate; Tamiflu [Roche] and in a labour case on influenza vaccines in healthcare workers in Canada. In 1997-99 Dr. Jefferson acted as a consultant for Roche,

in 2001-2 for GSK, and in 2003 for Sanofi-Synthelabo for pleconaril (an anti-rhinoviral, which did not get approval from the Food and Drug Administration). Dr. Jefferson was a consultant for IMS Health in 2013, and in 2014 was retained as a scientific adviser to a legal team acting on the drug Tamiflu (oseltamivir, Roche). In 2014-15, Dr. Jefferson was a member of two advisory boards for Boehringer. Dr. Jefferson has a potential financial conflict of interest in the investigation of the drug oseltamivir. Dr. Jefferson was a member of an Independent Data Monitoring Committee for a Sanofi Pasteur clinical trial. Dr. Jefferson is a co-signatory of the Nordic Cochrane Centre Complaint to the European Medicines Agency (EMA) over maladministration at the EMA in relation to the investigation of alleged harms of HPV vaccines and consequent complaints to the European Ombudsman.

Dr. Doshi received €1500 from the European Respiratory Society in support of his travel to the society's September 2012 annual congress in Vienna, where he gave an invited talk on oseltamivir. Dr. Doshi gratefully acknowledges the American Association of Colleges of Pharmacy for its funding support (\$11,000) for a study to analyze written medical information regarding the possible harms of statins. AACP had no involvement in the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of this manuscript. Dr. Doshi is also an associate editor of *The BMJ* (<http://www.bmj.com/about-bmj/editorial-staff/peter-doshi>) and an unpaid member of the IMEDS steering committee at the Reagan-Udall Foundation for the FDA, which focuses on drug safety research.

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Withholding Information on Unapproved Drug Marketing Applications: The Public Has a Right to Know

Sammy Almashat and Michael Carome

The U.S. Food and Drug Administration (FDA) is a critical public health agency that regulates drugs, medical devices, food, cosmetics, and tobacco products, which together amount to one-fifth of all U.S. economic activity.¹ However, much of the information upon which the agency relies when making pivotal regulatory decisions with regard to such products is withheld from the public.

One prominent example of the FDA's lack of transparency that has gained increasing attention in recent years concerns new drug applications (NDAs), including supplemental NDAs, that have been rejected by the agency or withdrawn by the company. The FDA's long-standing policy is that it does not release its analyses of data submitted for such applications or disclose agency complete response letters (CRLs) notifying drug manufacturers of the non-approval decisions and the reasons for such actions, nor does the agency even notify the public that such rejections or withdrawals have occurred.² If a company abandons or withdraws a drug marketing application before the FDA takes action on it, the FDA is technically required by law to disclose the safety and efficacy information in the application "upon request,"³ but the agency does not disclose the existence of such withdrawn or abandoned applications,⁴ which effectively renders moot this legal obligation.

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By contrast, the FDA routinely releases to the public its detailed analyses and findings related to data supporting the approval of a drug's first NDA and, upon request by at least three individuals, of supplemental NDAs for new uses of already marketed drugs.⁵

Need for, and Benefits of, Increased Transparency on Unapproved Drug Marketing Applications

The recent report *Blueprint for Transparency at the U.S. Food and Drug Administration* (hereafter referred to as "Blueprint report") highlights this issue, among other FDA transparency concerns.⁶ This report builds on the work of the FDA's 2010 Transparency Task Force, which made a number of recommendations to the agency, one of which was to release CRLs to shed light on why drug marketing applications were refused.⁷

The *Blueprint* report noted several potential benefits from releasing such information, including that "[t]he clinical community can benefit from the insight, expertise, and analyses of FDA reviewers, and researchers can learn from the failures of previous medical products in subsequent research programs."⁸

As detailed in the second focus area of the report, keeping the public in the dark about unapproved drug marketing applications prevents patients, researchers, and healthcare providers from gaining insight into why a drug's application was not approved.⁹ This lack of transparency is particularly troubling in cases where the FDA has found a currently marketed drug to be ineffective or unsafe for a newly proposed indication. Disclosure of the FDA's findings in such cases would promote public health by encouraging healthcare providers to avoid prescribing drugs for unapproved (off-label) uses that the agency has deemed to

be potentially dangerous or ineffective. This is especially important given the endemic practice within the pharmaceutical industry of illegally marketing drugs for off-label uses.¹⁰

Disclosure of CRLs is all the more important given the current permissive framework allowing the promotion of already marketed drugs for unapproved uses. Existing FDA guidance already permits drug and medical device manufacturers to market their products to physicians for unapproved uses through the dissemination of scientific or medical journal articles and reference publications.¹¹ The Medical Product Communications Act of 2017, which was introduced in the U.S. House of Representatives,¹² would further expand the scope of and permitted venues for off-label promotion while prohibiting the FDA from consider-

CRLs were disclosed in the companies' press releases. Disclosing all CRLs would allow the public, health-care professionals, and other interested stakeholders access to an unbiased rendering of the reasons for the FDA's rejection of a drug marketing application.

Finally, a new policy of transparency whereby the FDA discloses the existence of, and data related to, rejected applications for new drugs and new indications for already approved drugs also would be consistent with the Belmont Report's basic ethical principle of beneficence governing human subjects research.¹⁴ The beneficence principle establishes an ethical obligation to minimize possible harms and maximize potential benefits. In the event that a drug marketing application is rejected because the FDA determines that the drug's harms outweigh its benefits for a par-

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ing such off-label marketing activities as evidence of a manufacturer's "intended uses" for a drug or medical device. Such erosions of restrictions on off-label marketing make it vital that healthcare professionals be informed of off-label uses that were deemed by the FDA to be too dangerous or ineffective for patients.

Failing to provide information on unapproved NDAs also gives companies free rein to craft their own self-serving narratives as to why their product applications were turned down. A 2015 study by FDA researchers compared 61 of the FDA's CRLs issued to companies with the companies' press releases announcing the failed marketing applications.¹³ Unsurprisingly, the study found that in 11 (18%) of the 61 CRLs, companies did not issue a press release, and in 13 others (21%), the press release contained no information from the CRLs. Disturbingly, only 16% of the statements related to efficacy concerns and only 15% of the statements about safety concerns across all of the FDA

particular use, both the drug company and the FDA have an ethical obligation to make this determination public in order to avoid future clinical trials of the drug (or, in some cases, a similar drug in the same class) that would unnecessarily expose human subjects to harm. Other drugmakers can avoid such clinical trials only if they are made aware of all previous clinical trial data in a timely manner. Unfortunately, the medical literature is not a comprehensive or accurate source of such data.¹⁵

Feasibility: The FDA Should Follow Europe's and Canada's Lead

A policy whereby the FDA releases CRLs and the underlying analyses leading to the agency's decision not to approve a drugmaker's application is certainly feasible. In 2004, the European Union (EU) required that the European Medicines Agency (EMA) make publicly accessible "information about all refusals [of

human drug marketing applications] and the reasons for them.¹⁶ The same EU law also stipulated¹⁷ that for all drug applications withdrawn by the sponsor before the EMA has issued a decision on the application, the agency must publish public assessment reports containing the agency's analyses and conclusions related to the clinical data in the applications.¹⁸ In the latter case, the law made clear that such disclosures can only occur after the EMA removes all "commercially confidential" information from the public assessment reports of the withdrawn marketing applications. One can now search the EMA's website for all public assessment reports, with specific searches available for drugs that have been refused marketing authorization or that have been suspended or withdrawn after approval.¹⁹

Health Canada followed suit in 2015 when it announced that it would make available to the public all regulatory decision summaries, which contain the rationale for the agency's decisions on drug marketing applications.²⁰ This decision notably included, for public release, "final negative decisions and cancellations" for all marketing applications for new drugs and new indications for existing drugs.²¹ Similar to the European procedure, all regulatory decision summaries are now publicly searchable on Health Canada's website.²²

Thus, there exist one national and one multinational model of regulatory transparency to which the FDA can look for guidance should it choose to follow its sister agencies' lead by allowing the American public to, for the first time, learn when the FDA rejects a drug's marketing application and why it has done so.

Industry Argument Fails to Convince

To justify keeping the American public and health-care providers in the dark about the FDA's rejections of drug marketing applications, the pharmaceutical industry primarily has argued that disclosing such actions would reveal confidential commercial data and give other companies a competitive advantage. There are several reasons for rejecting this argument. First, a rejection by the FDA often occurs in parallel with a rejection by European or Canadian regulatory authorities, meaning that the failed marketing application and the reasons for the failure likely would become public knowledge anyway.

Second, although public disclosure of the FDA's rejection of one company's marketing application may allow competing companies to reap some monetary benefits by recalibrating similar research and development efforts, there is reason to believe that such disclosures would be economically advantageous to the industry in the aggregate. As the FDA's Transparency

Task Force pointed out in its 2010 report, disclosure of failed drug applications would allow other companies to more efficiently invest research monies into potentially more promising therapies.²³ Most companies eventually should benefit from such transparency.

Third, and most importantly, the current reality — in which companies remain unaware of a competitor's rejected drug marketing application for a similar product or use and, as a result, continue to invest research dollars and to expose human research subjects to potential harm in clinical trials that are likely to be futile — is unacceptable from both a public health and an ethical perspective.

Right to Know

The FDA must join the EMA and Health Canada in allowing the public to know when a drug is deemed unsafe or ineffective for a certain use. Even notwithstanding the public health benefits that disclosure of such information would reap, the public has a right to know when, how, and why the nation's largest public health agency reaches major decisions on the products it regulates. What former FDA Commissioner Dr. Donald Kennedy noted in 1978 still holds true: "[G]overnmental decisions, particularly regulatory decisions, should be based on publicly available information ... This premise underlies the Freedom of Information Act, the Federal Advisory Committee Act, and the Government in the Sunshine Act. In enacting each of these statutes, the Congress implemented a basic principle of our political system: that people affected by governmental decisions have a right to know the basis on which they are made. Anyone who questions the wisdom of a regulatory decision should be able to examine the factual foundation of the decision."²⁴

Note

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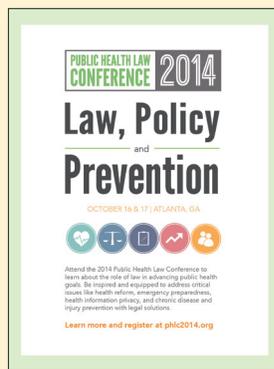
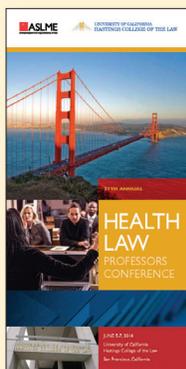
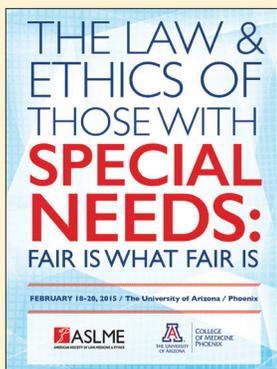
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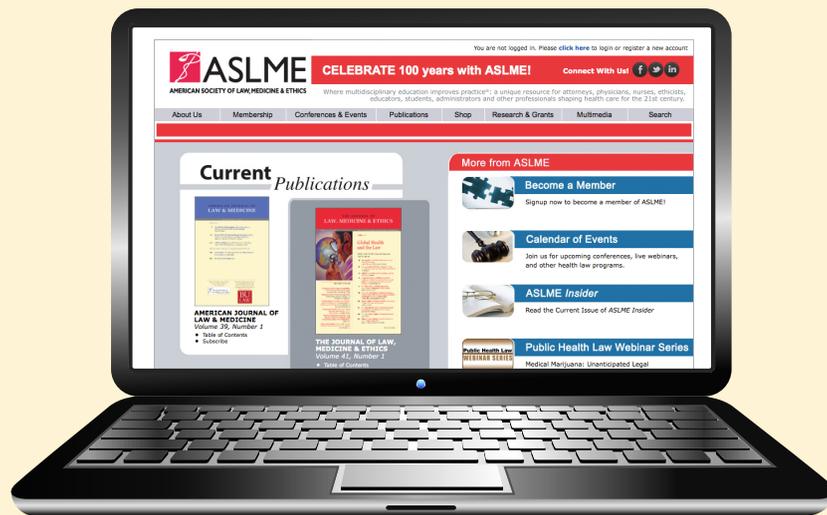
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