

**BLUEPRINT FOR TRANSPARENCY
AT THE
U.S. FOOD AND DRUG ADMINISTRATION**

**RECOMMENDATIONS TO ADVANCE THE DEVELOPMENT OF
SAFE AND EFFECTIVE MEDICAL PRODUCTS**

FDA TRANSPARENCY WORKING GROUP

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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

¹ U.S. Food and Drug Administration. FDA Transparency Initiative: Draft Proposals for Public Comment Regarding Disclosure Policies of the U.S. Food and Drug Administration. May 2010. Hereinafter "FDA TTFR."

² See FDA's Progress Report on the Transparency Initiative. Available at <http://www.fda.gov/AboutFDA/Transparency/TransparencyInitiative/ucm273854.htm>.

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

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;
- Faster innovation, as researchers, industry, and investors can more easily and thoroughly understand successes and failures;
- Improvements in FDA processes, with greater ability 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

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.

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

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.

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. Summary of the Blueprint for Transparency at FDA: 5 Focus Areas with 18 Specific Recommendations

Focus Areas	Recommendations from 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 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)
<p>FDA should disclose more of its own</p>	<ul style="list-style-type: none"> FDA should disclose communications to 	<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.

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).

<p>analysis and decision-making.</p>	<p>companies when products are not approved. (8)</p>	<p>FDA should issue guidance on the definition of abandonment. (9)</p> <ul style="list-style-type: none"> • 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. (10)
<p>FDA should disclose more about the application and review process for generic drugs and follow-on biologics.</p>	<ul style="list-style-type: none"> • FDA should disclose basic information about the filing of generic drug applications. (11) 	<ul style="list-style-type: none"> • FDA should disclose those portions of Complete Response Letters to generic drug manufacturers that relate to bioequivalence. (12) • FDA should 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 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)
<p>FDA should correct misleading information in the market.</p>		<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)
<p>FDA should disclose data from scientific studies to enhance understanding of medical products.</p>		<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, 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, 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.

Notice for Clinical Studies. 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

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).

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,

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). <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf> Accessed Aug. 23, 2016.

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.

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. 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

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. <http://www.fda.gov/forindustry/developingproductsforrareconditions/howtoapplyfororphanproductdesignation/default.htm>. Accessed Oct. 4, 2016.

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). <http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM393978.pdf> Accessed Sept. 6, 2016.

¹⁸ Pub. Law 114-255 (Dec. 13, 2016), §3051.

¹⁹ FDCA 505A, 21 U.S.C. §355a.

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.

With respect to pediatric exclusivity, the Best Pharmaceuticals for Children Act includes provisions that provide public access to information regarding written requests, safety

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. Aug. 2008. <http://www.fda.gov/downloads/regulatoryinformation/guidances/ucm125650.pdf> Accessed Sept. 8, 2016.

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. Technical Definition of iodine I 131 monoclonal antibody 8H9. <https://www.cancer.gov/publications/dictionaries/cancer-drug?cdrid=380753>. Accessed Oct. 5, 2016.

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 public 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

²⁵ FDA TTFR Draft Proposals at page 37.

²⁶ FDA TTFR Draft Proposals 8, 9 and 10.

²⁷ These include Informa PLC, IMS Health, Evaluate Group, Pharmaprojects, and Springer Nature.

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. 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.

²⁸ PAREXEL International. Biopharmaceutical R&D Statistical Sourcebook 2012/2013. Parexel International Corp., 2012.

²⁹ European Medicines Agency. Guide to information on human medicines evaluated by European Medicines Agency: What the Agency publishes and when. http://www.ema.europa.eu/docs/en_GB/document_library/Other/2016/05/WC500206484.pdf Accessed September 30, 2016.

- 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

³⁰ *E.g.*, Juno Therapeutics Places JCAR015 Phase II ROCKET Trial on Clinical Hold. Nov. 23, 2016. <http://ir.junotherapeutics.com/phoenix.zhtml?c=253828&p=irol-newsArticle&ID=2225491>. Accessed Dec. 14, 2016.

³¹ Typically, companies provide information about clinical holds without comment from FDA. See *e.g.* FDA Places some Seattle Genetics drug trials on hold after four deaths. Reuters. 27 December 2016.

studies. FDA should also disclose documents that memorialize acceptable changes to the initial request.³²

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.

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 Bourgeois FT, Hwang TJ. The Pediatric Research Equity Act Moves Into Adolescence. *JAMA*. 2017;317(3):259-260.

³³ FDA TTFR Proposals 8, 9, and 10.

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 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.

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

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.

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 decisionmaking. For supplemental indications, FDA releases its memos under the Freedom of Information Act and posts the memos if three requests are received.³⁶

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:

“(l)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.*”

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

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 Kesselheim AS, Mello MM. Confidentiality Laws And Secrecy In Medical Research: Improving Public Access To Data On Drug Safety. *Health Aff* 2007;26(2):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 Information 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.

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 view of the safety of products with 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

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.

⁴⁰ FDA TTFR Proposals 11, 12, 13, & 15.

⁴¹ Lurie P, Chahal HS, Sigelman DW, Stacy S, Sclar J, Ddamulira B. Comparison of content of FDA letters not approving applications for new drugs and associated announcements from sponsors: cross sectional study. *BMJ* 2015;350:h2758, doi:101136/bmj.h2758.

⁴² Securities Exchange Commission. Press Release: Biotech Company Misled Investors About New Drug’s Status With FDA. March 29, 2016. <https://www.sec.gov/news/pressrelease/2016-59.html>

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

Accessed Aug. 31, 2016 (charging AVEO Pharmaceuticals with violations of federal securities laws by omitting to disclose to investors that FDA had called for new clinical trial).

⁴³ EMA. European public assessment reports: background & context. http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/general/general_content_000433.jsp&mid=WC0b01ac058067fa25 Accessed Sept. 8, 2016.

⁴⁴ *E.g.*, European Medicines Agency Committee for Medicinal Products for Human Use. dasiprotimut-t Assessment Report EMA/314727/2015 (April 23, 2015). http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/002772/WC500190039.pdf. Accessed Dec. 14, 2016.

⁴⁵ FDA. Availability of Masked & Deidentified Non-Summary Safety & Efficacy Data; Request for Comments. 78 (107) FED. REG. 33421, at 33422 (June 4, 2013).

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 Repository⁴⁶ with established procedures for de-identification of data and sharing data with responsible researchers for legitimate

⁴⁶ NHLBI Biologic Specimen & Data Repository Coordinating Center (BioLINCC). <https://biolincc.nhlbi.nih.gov/home/> Accessed Sept. 7, 2016.

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.

⁴⁷ Coady SA, Wagner E. Sharing individual level data from observational studies and clinical trials: a perspective from NHLBI. *Trials* 2013;14:201.

⁴⁸ FDA TTFR Proposals 11, 12, 13, and 15.

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.^{51,52} 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.⁵³ Congress modeled this “biosimilars” legislation on the 1984 Hatch-Waxman Act that created an effective pathway for FDA to approve generic drugs.

⁴⁹ Generic Pharmaceutical Association (GPhA). Generic Drug Savings in the U.S. (2015). http://www.gphaonline.org/media/wysiwyg/PDF/GPhA_Savings_Report_2015.pdf. Accessed Sept. 8, 2016.

⁵⁰ A generic drug is approved based on its ‘bioequivalence’ to a previously approved drug, which is known as the ‘Reference Listed Drug’ (RLD).

⁵¹ Special Committee on Aging, U.S. Senate. Sudden Price Spikes in Off-Patent Prescription Drugs: The Monopoly Business Model that Harms Patients, Taxpayers, and the U.S. Health Care System. December 2016.

⁵² Gupta R, Kesselheim AS, Downing N, Greene J, Ross JS. Generic Drug Approvals Since the 1984 Hatch-Waxman Act. *JAMA Intern Med.* 2016 Sep 1;176(9):1391-3.

⁵³ Public Health Service Act §351(k), 42 U.S.C. §262(k).

Current FDA Practice Related to Transparency. FDA generally does not release information on which companies have filed generic drug applications, and for which drugs.⁵⁴ 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.⁵⁵ 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.”⁵⁶

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

⁵⁴ FDA does post applications related to Paragraph IV Patent Certifications, which are submissions made one year before the expiration of data exclusivity protections. However, information naming the individual applicants is not disclosed. Available at <http://www.fda.gov/downloads/drugs/developmentapprovalprocess/howdrugsaredevelopedandapproved/approvalapplications/abbreviatednewdrugapplicationandagenerics/ucm293268.pdf>.

⁵⁵ FDA TTFR Draft Proposal 10. The Task Force did not address biosimilars, which Congress had authorized only two months before release of the TTFR.

⁵⁶ FDA TTFR pp. 47-48.

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 controversy 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.⁵⁷ 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.⁵⁸

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.

⁵⁷ Helfand C. FDA swats down Teva's EpiPen copy, putting Mylan in cruise control. Fierce Pharma. 1 March 2016. <http://www.fiercepharma.com/sales-and-marketing/fda-swats-down-teva-s-epipen-copy-putting-mylan-cruise-control>. Accessed Sept. 10, 2016.

⁵⁸ *Wall Street Journal*. Anaphylactic Political Shock. Editorial. 24 August 2016.

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.⁵⁹
12. FDA should disclose those portions of Complete Response Letters to generic drug manufacturers that relate to bioequivalence (as compared to manufacturing processes).
13. FDA should 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 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

⁵⁹ FDA TTFR Draft Proposal 10.

Commission about a patent claiming that an as-yet unpublished safety study had a “positive 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.⁶⁰

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.⁶¹ 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 applicant announced the post-hoc results, generating considerable public attention.”⁶²

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

⁶⁰ Sharfstein JM, Psaty BM. Evaluation of the Cardiovascular Risk of Naltrexone-Bupropion: A Study Interrupted. *JAMA*. 2016 Mar 8;315(10):984-6.

⁶¹ Kesselheim AS, Avorn J. Approving a Problematic Muscular Dystrophy Drug: Implications for FDA Policy. *JAMA*. 2016 Dec 13;316(22):2357-2358.

⁶² Minutes of the Meeting of the Peripheral and Central Nervous System Drugs Advisory Committee. Center for Drug Evaluation and Research. FDA. 25 April 2016, p. 222. <http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PeripheralandCentralNervousSystemDrugsAdvisoryCommittee/UCM510390.pdf>, Accessed December 31, 2016.

companies to make statements about non-FDA-approved uses of available products.^{63,64}

Current FDA Practice Related to Transparency. As practice now stands, companies have wide latitude to characterize data submitted to FDA or their 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.”⁶⁵ 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).”⁶⁶ It was further recommended that FDA correct misleading information about the product that is the subject of the application.⁶⁷

⁶³ Sharfstein JM, Charo A. The Promotion of Medical Products in the 21st Century: Off-label Marketing and First Amendment Concerns. *JAMA*. 2015 Nov 3;314(17):1795-6.

⁶⁴ Avorn J, Sarpatwari A, Kesselheim AS. Forbidden and Permitted Statements about Medications--Loosening the Rules. *N Engl J Med*. 2015 Sep 3;373(10):967-73.

⁶⁵ 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.

⁶⁶ FDA TTFR p. 49.

⁶⁷ FDA TTFR Draft Proposal 16.

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 consider 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 during 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.⁶⁸ 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).⁶⁹ In other circumstances, a sponsor may make a commitment to FDA to conduct post-approval studies (Postmarket Commitments).⁷⁰ Similarly, for certain devices, FDA may require post-approval

⁶⁸ International Conference on Harmonisation (ICH). Guidance for Industry: Structure & Content of Clinical Study Reports (July 1996). <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073113.pdf> Accessed Sept. 7, 2016.

⁶⁹ FDCA §505(o), 21 U.S.C. §355(o) (PMRs for drugs and biologics).

⁷⁰ FDCA §506B, 21 U.S.C. §356b (PMCs for drugs and biologics).

studies.⁷¹ 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.⁷² 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.⁷³

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.⁷⁴

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

⁷¹ Reynolds IS, Rising JP, Coukell AJ, Paulson KH, Redberg RF. Assessing the Safety and Effectiveness of Devices After US Food and Drug Administration Approval: FDA-Mandated Postapproval Studies. *JAMA Intern Med* 2014;174(11):1773-1779. FDCA §522, 21 U.S.C. §3601 (device surveillance studies); 21 C.F.R. §814.82 & §814.126 (post approval studies for PMA and Humanitarian Use devices).

⁷² In appropriate circumstances, such as in medical product reviews and safety warnings, FDA has released nonsummary data and information from clinical and nonclinical trials. FDA does disclose information on the status of postmarket requirements, postmarket commitments, and post-approval device studies. FDA. Postmarketing Requirements and Commitments: Reports. <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Post-marketingPhaseIVCommitments/ucm064436.htm>. Accessed Dec. 5, 2016. FDA. Post-approval Studies. <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/PostmarketRequirements/PostApprovalStudies/default.htm>. Accessed Dec. 5, 2016 at <http://www.fda.gov/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm070974.htm>

⁷³ 21 C.F.R. §314.430(c) (prohibiting release of data or information from unapproved applications if the existence of the application has not been publicly acknowledged); §314.430(e)(2)(summaries released after approval “do not constitute the full reports of investigations...on which the safety and effectiveness of the drug may be approved”).

⁷⁴ FDA TTFR Draft Proposal 17.

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.”⁷⁵

Some pharmaceutical companies, such as GlaxoSmithKline and Johnson and Johnson, have taken leading roles in enabling independent investigators to submit requests to access some clinical trial data, subject to certain conditions.⁷⁶ One repository of the clinical trials for which investigators may request access is the Clinical Study Data Request website.⁷⁷ 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.⁷⁸

In October 2014, the European Medicines Agency adopted a new policy on disclosure of Clinical Study Reports submitted in marketing applications after January 1, 2015.⁷⁹ In October 2016, the agency, pursuant to this policy, for the first time posted on its website

⁷⁵ Institute of Medicine. (2015). *Sharing clinical trial data: maximizing benefits, minimizing risk*. <https://www.nap.edu/catalog/18998/sharing-clinical-trial-data-maximizing-benefits-minimizing-risk> Accessed December 31, 2016. See also Krumholz HM, Bourne PE, Kuntz RE, et al. Data acquisition, curation and use for a continuously learning health system: A vital direction for health and health care. National Academy of Medicine. 19 September 2016.

⁷⁶ Mello, MM, Francer, JK, Wilenzick M, Teden P, Bierer BE, Barnes M. Preparing for Responsible Sharing of Clinical Trial Data. *N Engl J Med* 2013;369 (17):1651-1658; PhRMA & European Federation of Pharmaceutical Industries & Associations (EFPIA). Principles for Responsible Data Sharing: Our Commitment to Patients & Researchers (July 18, 2013). <http://phrma.org/sites/default/files/pdf/PhRMAPrinciplesForResponsibleClinicalTrialDataSharing.pdf> Accessed Aug. 29, 2016. See also the Yale University Open Data Access (YODA) Project. <http://yoda.yale.edu/>.

⁷⁷ <https://clinicalstudydatarequest.com>. Accessed Dec. 18, 2016.

⁷⁸ Boutron I, Dechartres A, Baron G, Li J, Ravaud P. Sharing of Data From Industry-Funded Registered Clinical Trials. *JAMA* 2016;315(24):2729-2730.

⁷⁹ European Medicines Agency. Policy on publication of clinical data for medicinal products for human use (Policy 0070). Oct. 2, 2014. http://www.ema.europa.eu/docs/en_GB/document_library/Other/2014/10/WC500174796.pdf Accessed Sept. 7, 2106.

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.⁸⁰ 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.⁸¹

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.⁸²

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,⁸³ a repository with established procedures for de-identification of data and sharing data

⁸⁰ *Id.*

⁸¹ European Union General Court. PTC Therapeutics v. EMA, Docket T-718/15 R (interim injunction issued July 20, 2016). <http://curia.europa.eu/juris/document/document.jsf?jsessionid=9ea7d0f130d563aba6d1dc504c2eaf15e2493e2b78e6.e34KaxiLc3eQc40LaxqMbN4Pa3qRe0?text=&docid=181921&pageIndex=0&doclang=EN&mode=lst&dir=&occ=first&part=1&cid=1110073>. Accessed Dec. 17, 2016.

⁸² Guidance for Industry, Postmarketing Studies and Clinical Trials – Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act. <http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm172001.pdf>

⁸³ NHLBI Biologic Specimen & Data Repository Coordinating Center (BioLINCC). <https://biolincc.nhlbi.nih.gov/home/> Accessed Sept. 7, 2016.

with responsible researchers for legitimate scientific investigations.⁸⁴ 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 ClinicalTrial.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

⁸⁴ Coady SA, Wagner E. Sharing individual level data from observational studies and clinical trials: a perspective from NHLBI. *Trials* 2013;14:201.

the extent possible, FDA should harmonize standards on Clinical Study Reports release with the European Medicines Agency.⁸⁵

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

⁸⁵ The European Medicines Agency aims to publish marketing authorizations, line extensions, and extensions of product indication applications 60 days after the European Commission decision and following the publication of the European Public Assessment Report (EPAR). Withdrawn applications are published 150 days after the receipt of the withdrawal letter. European Medicines Agency – Marketing authorization – Clinical data publication

http://www.ema.europa.eu/ema/?curl=pages/special_topics/general/general_content_000555.jsp.

Accessed Jan. 17, 2016.

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."⁸⁶

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 help inform companies about what it takes 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

⁸⁶ PhRMA. Comments on Food and Drug Administration Transparency Task Force. 7 August 2009.

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. 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. However, 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 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 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 (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 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 the effort. Greater transparency at FDA will lead to safer and more effective medical products, with lasting benefits for clinical care, scientific progress, and public health.