



Public Interest Comment

Comments submitted to the Food and Drug Administration in the Matter of:

Benefit-Risk Assessments in Drug Regulatory Decision-Making

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Executive Summary

The Food and Drug Administration’s Draft PDUFA V Implementation Plan provides a welcome set of recommendations for modernizing the Agency’s IT infrastructure and accommodating the need for electronic submissions of new drug applications. However, the plan fails to effectively communicate the benefits and risks associated with new drug approvals by ignoring the fundamental lack of clarity regarding the standards by which the Agency determines a drug’s “safety” and “effectiveness.”

In order to meet its statutory obligations under the Food and Drug Administration Safety and Innovation Act, we offer a number of recommendations that can improve the Agency’s Draft PDUFA V Implementation Plan: (1) narrow pre-market approval considerations to safety and effectiveness, not hypothetical off-label uses; (2) clarify the specific standards for what constitutes a “safe” and “effective” drug; (3) limit the use of the structured benefit-risk assessment laid out in the Draft PDUFA V Implementation Plan to the post-market approval process; and (4) move to embrace a tiered order of effectiveness model for new drug approvals.

The Niskanen Center is a 501(c)3 libertarian issue advocacy organization that works to change public policy through direct engagement in the policymaking process.

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Introduction

As the Food and Drug Administration (FDA) noted in its 2014-2018 Strategic Planning Document:

To keep the public trust and maintain FDA's global leadership role in fostering innovation, FDA must employ "smart regulation". By "smart regulation" we mean that FDA can attain the goal of protecting the public health while encouraging innovation. That is, the goal can be reached through smart, sound, science-based regulation that imposes the most appropriate regulatory framework while minimizing unnecessary burden.¹

Although the FDA ostensibly embraces the need for "smart regulation," the structured benefit-risk assessment framework laid out in the Draft Prescription Drug User Fee Act (PDUFA) V Implementation Plan² fails to minimize the "unnecessary burden" imposed on regulatory approvals for new drugs by failing to achieve the goal of communicating the benefit-risk calculation of approval decisions.

The Food and Drug Administration Safety and Innovation Act (FDASIA), as it amends the Federal Food Drug and Cosmetic Act, directs the FDA to "implement a structured risk-benefit assessment framework" in order to produce "a consistent and systematic approach to the discussion and regulatory decisionmaking, and the communication of the benefits and risks of new drugs."³ While the Draft PDUFA V Implementation Plan does indeed lay out a "systematic approach" to rationalizing the FDA's decision-making process, the specific standards by which the FDA makes its approval decisions remain unclear. So long as that opacity remains embedded in the new drug approval process, the PDUFA V Implementation Plan cannot possibly comply with the "communication of the benefits and risks of new drugs" provision of FDASIA.

These comments will discuss issues related to the "exploration of methods to advance structured benefit-risk assessment," as described in the request for comments.⁴ However, much of the focus is on recommendations for how the FDA can better clarify its standards for pre-market drug approvals. So long as the FDA's standards for determining "safety and effectiveness" remain unclear, any application of the Draft PDUFA V Implementation Plan cannot meet its statutory obligation under FDASIA to communicate the benefits and risks of new drugs.

¹ "FDA Strategic Priorities 2014-2018," Food and Drug Administration, September 2014, p. 9, <https://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Reports/UCM416602.pdf>.

² "Structured Approach to Benefit-Risk Assessment in Drug Regulatory Decision-Making," Draft PDUFA V Implementation Plan (FY 2013-2017), Food and Drug Administration, February 2013, <http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM329758.pdf>.

³ 21 U.S.C. § 355(d), <https://www.law.cornell.edu/uscode/text/21/355>. ("The Secretary shall implement a structured risk-benefit assessment framework in the new drug approval process to facilitate the balanced consideration of benefits and risks, a consistent and systematic approach to the discussion and regulatory decisionmaking, and the communication of the benefits and risks of new drugs. Nothing in the preceding sentence shall alter the criteria for evaluating an application for marketing approval of a drug.")

⁴ "Benefit-Risk Assessments in Drug Regulatory Decision-Making," Food and Drug Administration, Docket No. FDA-2017-N-4076, posted August 9, 2017, <https://www.regulations.gov/document?D=FDA-2017-N-4076-0001>.

What the Structured Benefit-Risk Assessment Overlooks

As stated in the FDA's 2014-2018 Strategic Priorities report, the goal of the Agency's new review model "is to improve the efficiency and effectiveness of the first cycle review process and decrease the number of review cycles necessary for approval, ensuring that patients have timely access to safe, effective, and high quality new drugs and biologics."⁵ However, if the goal is truly improved "efficiency and effectiveness" that results in "timely access to safe, effective, and high quality new drugs" for patients, then this framework fails to address the underlying drivers of approval delays.

Instead, the structured framework focus on upgrading the FDA's regulatory approval pipeline and modernizing its IT infrastructure to better accommodate electronic submissions. Although such mechanisms can certainly help speed the review process for new drug approvals and biological license applications, the fundamental roadblocks to expediting such approvals remain unaddressed. These include:

1. Utilizing non-specific standards in determining the "safety" and "effectiveness" of a new drug;
2. Predicating new drug approvals, in part, on hypothetical considerations of how the drug might be used in off-label contexts; and
3. Applying benefit-risk assessments to pre-market approval analyses.

Until these problems are addressed, the FDA cannot possibly meet the requirements of the structured benefit-risk assessment framework.

Safety and Effectiveness Standards: "Life Outcomes" for the "Average Patient"

Under 21 U.S.C. § 314.125(b),⁶ the FDA is permitted to refuse the application of a new drug for a number of reasons, including:

(2) The investigations required under section 505(b) of the Federal Food, Drug, and Cosmetic Act⁷ do not include adequate tests by all methods reasonably applicable to

⁵ PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2013 Through 2017, Food and Drug Administration, p. 6,

<https://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM270412.pdf>.

⁶ 21 U.S.C. § 314.125(b), <https://www.law.cornell.edu/cfr/text/21/314.125>.

⁷ This section refers to the 505(b) application for a new drug approval that relies in part on either (1) published literature, investigations, or other source(s) referencing specific information necessary to the approval of the application, but for which the applicant does not possess a "right of reference" and/or (2) when approval of the application relies on a previous finding of safety and/or effectiveness as determined by the FDA. See 21 U.S.C. § 314.107, <https://www.law.cornell.edu/cfr/text/21/314.107>; See also "Guidance for Industry: Applications Covered by Section 505(b)(2)," Draft Guidance, Food and Drug Administration, October 1999, <https://www.fda.gov/downloads/Drugs/Guidances/ucm079345.pdf>.

show whether or not the drug is safe for use under the conditions prescribed, recommended, or suggested in its proposed labeling.

(3) The results of the tests show that the drug is unsafe for use under the conditions prescribed, recommended, or suggested in its proposed labeling or the results do not show that the drug product is safe for use under those conditions.

(4) There is insufficient information about the drug to determine whether the product is safe for use under the conditions prescribed, recommended, or suggested in its proposed labeling.

(5) There is a lack of substantial evidence⁸ consisting of adequate and well-controlled investigations, as defined in § 314.126,⁹ that the drug product will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in its proposed labeling. ...

(15) A nonclinical laboratory study that is described in the [new drug application] and that is essential to show that the drug is safe for use under the conditions prescribed, recommended, or suggested in its proposed labeling was not conducted in compliance with the good laboratory practice regulations in part 58 of this chapter and no reason for the noncompliance is provided or, if it is, the differences between the practices used in conducting the study and the good laboratory practice regulations do not support the validity of the study.

These provisions are the bulk of the statutory scope under which a new drug may be denied approval for reasons related to safety. Although the law provides these general guidelines for determining reasons to *deny* a new drug application approval, the details for determining a grant of *approval* are by default left to the FDA's purview. Those specifics have been disparately catalogued by the FDA in various guidance documents issued to help illuminate the Agency's thinking on how it determines safety and

⁸ "Substantial evidence" is defined as "evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof." Additionally, the Secretary of Health and Human Services is granted the authority to make a finding that information provided "based on relevant science ... from one adequate and well-controlled clinical investigation and confirmatory evidence (obtained prior to or after such investigation)" is "sufficient to establish effectiveness" and "may consider such data and evidence to constitute substantial evidence." See 21 U.S.C. § 355(d), <https://www.law.cornell.edu/uscode/text/21/355>.

⁹ This section outlines what constitutes an "adequate and well-controlled investigation," recognizing that: "adequate and well-controlled investigations provide the primary basis for determining whether there is 'substantial evidence' to support the claims of effectiveness for new drugs. Therefore, the study report should provide sufficient details of study design, conduct, and analysis to allow critical evaluation and a determination of whether the characteristics of an adequate and well-controlled study are present." See 21 U.S.C. § 314.126 (a), <https://www.law.cornell.edu/cfr/text/21/314.126>.

effectiveness for new drug approvals.¹⁰ Additionally, the Congressional Research Service (CRS) has noted the FDA's broad latitude in making assessments for what qualifies as evidence of safety and effectiveness.¹¹ While the CRS report does include definitions for "safety, efficacy, and effectiveness," they are pulled from a dictionary for epidemiologic terms—not from any FDA draft guidance, rules, or statute.¹²

The difficulties of defining clear standards for safety and effectiveness has led to an understandably complicated regime, under which even the FDA admits that: "In the end, no matter how much data are available, we often have to make a judgment call, weighing the known benefits against known risks and the potential—and possibly unknown—risks."¹³ In order to make these judgment calls, the FDA most relies on assessments of how a new drug will effect an "average patient."

Although the phrase "average patient" is not mentioned in regulatory guidance documents or statutes, a 2009 report from the University of Chicago suggests that this is indeed the default means by which

¹⁰ See "Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products," U.S. Department of Health and Human Services, Food and Drug Administration, May 1998, <https://www.fda.gov/ohrms/dockets/dockets/98p0311/Tab0035.pdf>; See also "Guidance for Industry and Investigators: Safety Reporting Requirements for INDs and BA/BE Studies," U.S. Department of Health and Human Services, Food and Drug Administration, December 2012, <https://www.fda.gov/downloads/Drugs/Guidances/UCM227351.pdf>; See also "Manual of Policies and Procedures," Food and Drug Administration, Center for Drug Evaluation and Research, MAPP 6010.3 Rev. 1, <https://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ManualofPoliciesProcedures/UCM080121.pdf>.

¹¹ Susan Thaul, "How the FDA Approves Drugs and Regulates Their Safety and Effectiveness," Congressional Research Service, R41983, June 25, 2012, p. 5, <https://fas.org/sgp/crs/misc/R41983.pdf>. ("The [Federal Food, Drug, and Cosmetic Act] requires 'substantial evidence' of drug safety and effectiveness. FDA has interpreted this term to mean that the manufacturer must provide at least two adequate and well-controlled Phase III clinical studies, each providing convincing evidence of effectiveness. The agency, however, exercises flexibility in what it requires as evidence. As its regulations describe in detail, FDA can assess safety and effectiveness in a variety of ways, relying on combinations of studies by the manufacturer and reports of other studies in the medical literature.")

¹² Thaul, p. 4. ("*Safety* is often measured by toxicity testing to determine the highest tolerable dose or the optimal dose of a drug needed to achieve the desired benefit. Studies that look at safety also seek to identify any potential adverse effects that may result from exposure to the drug. *Efficacy* refers to whether a drug demonstrates a health benefit over a placebo or other intervention when tested in an ideal situation, such as a tightly controlled clinical trial. *Effectiveness* describes how the drug works in a real-world situation. Effectiveness is often lower than efficacy because of interactions with other medications or health conditions of the patient, sufficient dose or duration of use not prescribed by the physician or followed by the patient, or use for an off-label condition that had not been tested.")

¹³ "How FDA Evaluates Regulated Products: Drugs," Food and Drug Administration, accessed August 28, 2017, <https://www.fda.gov/AboutFDA/Transparency/Basics/ucm269834.htm>.

determinations of safety are made.¹⁴ This conclusion is drawn from industry guidelines the FDA itself released.¹⁵ The authors note that,

*[a]lthough regulations do not spell out exactly the evidentiary standard to which the FDA holds a new drug, the FDA has issued a guidance that emphasizes a drug should [sic] evaluated based on all the patients that enroll in a trial and that requires the rate of false positive findings to be set to 5 percent.*¹⁶

The use of the “average patient” standard for approval reviews then lends itself to the Agency’s search for evidence of purported clinical utility—that is, attempting to discern “life outcomes” in patients.¹⁷ The Agency is operating under an assumption that attempting to discern the “true outcomes for patients”¹⁸ (that is, “life outcomes”) is the appropriate scope of focus for FDA approval reviews. It is not, for a number of reasons.

First, the standard itself, as some researchers have noted, is elusive.¹⁹ There is no codified definition of clinical utility that can be objectively measured and, therefore, cannot be effectively communicated through the proposed benefit-risk assessment framework.²⁰ Even within the scientific community, the

¹⁴ Mark Van Der Laan, Anup Malani, and Oliver Van Der Bembom, “Accounting for Differences among Patients in the FDA Approval Process,” University of Chicago Law School, John M. Olin Law & Economics Working Paper No. 488, Public Law and Legal Theory Working Paper No. 281, October 2009, p. 6, http://chicagounbound.uchicago.edu/cgi/viewcontent.cgi?article=1013&context=public_law_and_legal_theory. (“The implication—borne out by practice—is that the FDA judges the efficacy of a drug by the difference between average outcomes in the treatment and control arms of a trial.”)

¹⁵ “Guidance for Industry: E9 Statistical Principles for Clinical Trials,” U.S. Department of Health and Human Services, Food and Drug Administration, September 1998, <https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm073137.pdf>.

¹⁶ Van Der Laan, et. al., p. 6.

¹⁷ Joseph V. Gulfo and Jason Briggeman, “Fostering Resilience in the Medical Marketplace: A Plan for Reform of Pharmaceutical Regulation,” Farleigh Dickinson University, Initiative for Patient-Centered Innovation, p. 9, footnote 15, (forthcoming). (“The amount of variation in patient responses that can be represented in preapproval trials is extremely limited, and so when purporting to assess a drug’s clinical utility, the FDA by necessity uses a construct of an ‘average patient.’ So even though patient responses—and also patient preferences, such as tolerance for risk—vary greatly, if FDA predicts that its ‘average patient’ will not benefit from a drug, the drug is barred from the medical marketplace.”)

¹⁸ Draft PDUFA V Implementation Plan, p. 2.

¹⁹ Gulfo and Briggeman, “Fostering Resilience,” p. 8. (“Clinical utility is an elusive standard—it is tantamount to proving that there are, in some overall and ultimate sense, benefits to patient health from a product. Generally, even the best science cannot produce conclusive evidence on such a question, as attested by the many conflicting studies of the health effects of aspirin, for example. Aspirin is a safe and effective product, when used in accordance with its labeling—it generally delivers the promised effect to alleviate pain—but scientists continue even today to investigate whether taking aspirin is ultimately ‘good’ with regard to different health risks, for different types of patients, over the long run, and so forth. ... If we do not have the answers on ultimate patient outcomes from taking aspirin ... there is little chance of correctly identifying ultimate health outcomes from any given new drug.”)

²⁰ The one exception is in a draft FDA concept paper on drug-diagnostic co-development from 2005. In the glossary, the paper listed a definition of “clinical utility” as “[t]he elements that need to be considered when evaluating the risks and benefits in diagnosing or predicting risk for an event (drug response, presence or risk of a health condition).” Precisely what those “elements” are to include are unclear and there is no indication that the

specifics of the concept are debated, with some arguing that “there is no consensus on its definition or how to robustly demonstrate it to the satisfaction of multiple stakeholders.”²¹ However, even if metrics could be codified, it’s unclear that clinical utility or “life outcomes” could be empirically established in the context of pre-market approval.

This leads to the second problem with the FDA’s focus on clinical utility and “life outcomes.” Predicating determinations of safety and effectiveness on “life outcomes” requires more data than should otherwise be necessary. As a result, clinical trials take longer to complete and add additional, and unnecessary, layers of complexity to the approval process.²² And even then, the conclusions are often even less certain than results from more narrowly-focused trials attempting to determine whether a drug shows positive biological activity in a disease treatment. Thus, larger clinical trial sizes do not necessarily yield the optimal amount (or type) of data required for the FDA to determine a drug’s safety.²³

Finally, the multifactorial nature of diseases makes it difficult to establish clear and informative empirics regarding what constitutes acceptable “life outcomes” for patients. It also calls into question whether clinical trials, rather than real-world experimentation overseen by doctors with patient feedback, are the appropriate venue for making such decisions. Unfortunately, this approach of “judging drugs largely on the basis of average treatment effects ... implicitly assumes that doctors are very bad at matching the right patient subgroups to drugs.”²⁴

guidance, specifically labelled “not for implementation,” was ever formally adopted as FDA regulatory guidance. “Drug-Diagnostic Co-Development Concept Paper,” Food and Drug Administration, April 2005, <https://www.fda.gov/downloads/drugs/scienceresearch/researchareas/pharmacogenetics/ucm116689.pdf>.

²¹ L.J. Lesko, I. Zineh, and S-M Huang, “What is Clinical Utility and Why Should We Care?,” *Clinical Pharmacology & Therapeutics*, Vol. 88(6), December 2010.

²² Joseph V. Gulfo, Jason Briggeman, and Ethan C. Roberts, “The Proper Role of the FDA for the 21st Century,” Mercatus Center, February 2016, p. 9-10, <https://www.mercatus.org/system/files/Gulfo-Proper-Role-FDA-v1.pdf>. (“Such outcomes-focused trials, which must be lengthy as well as broad, are far more uncertain in their conclusions than are trials that aim to show that a drug has biological activity related to a disease and is safe to use in that setting. For example, a cholesterol drug may safely improve cholesterol levels for a given patient, but a trial may not show the drug to have positive effects on outcomes such as the patient’s lifespan. This does not mean, however, that the drug should be denied to all patients it could help.”)

²³ See John P. A. Ioannidis, MD, “Contradicted and Initially Stronger Effects in Highly Cited Clinical Research,” *Journal of the American Medical Association*, Vol. 294, No. 2, pp. 218-228, July 13, 2005, <http://jamanetwork.com/journals/jama/fullarticle/201218>. (“A perfect gold standard is not possible in clinical research, so we can only interpret results of studies relative to other studies. Whenever new research fails to replicate early claims for efficacy or suggests that efficacy is more limited than previously thought, it is not necessary that the original studies were totally wrong and the newer ones are correct simply because they are larger or better controlled. Alternative explanations for these discrepancies may include differences in disease spectrum, eligibility criteria, or the use of concomitant interventions.”); See also Joseph Lau, John P. A. Ioannidis, and Christopher H. Schmid, “Summing up evidence: one answer is not always enough,” *The Lancet*, Vol. 351, pp. 123-127, January 10, 1998, [http://www.thelancet.com/pdfs/journals/lancet/PIIS0140-6736\(97\)08468-7.pdf](http://www.thelancet.com/pdfs/journals/lancet/PIIS0140-6736(97)08468-7.pdf). (“Large trials, while more precise than smaller trials, may miss important treatment variation and may not be any more generalisable than smaller studies unless their inclusion criteria and recruitment capture broad populations and different settings. Thus, if we want to evaluate how a treatment works, we must ask first whether the best answer is a single estimate, or separate estimates for individuals or subgroups of patients.”)

²⁴ Van Der Laan, et. al., p. 8.

The complexities created by applying these standards to new drug approvals is further compounded by the FDA’s willingness to consider other hypotheticals, such as how individuals might potentially use approved drugs in off-label contexts.

Unnecessary Considerations of Off-Label Use

In addition to the complications arising from a focus on clinical utility and “life outcomes” for the “average patient” standards, the regulatory pipeline is further cluttered by the FDA’s considerations of off-label use—drugs that may be prescribed for a use other than that for which they have been approved.²⁵ Such uses are common and legally permitted for FDA-approved drugs. However, in clinical trials for approval of new drugs, the FDA often speculates on potential off-label uses in making determinations of safety. Indeed, the Draft PDUFA V Implementation Plan notes that one of the factors “that inform the regulatory decision” to approve a new drug “consists of identifying facts as well as uncertainties and any assumptions that need to be made to deal with what is not known.”²⁶

This assumption—that it is necessary to address questions of “what is not known”—is never questioned in the benefit-risk assessment framework. In fact, the Draft PDUFA V Implementation Plan suggests that the FDA shoulders a responsibility for attempting to guess at these types of outcomes:

*Beyond the clinical study of drugs, the Agency must also consider how people will actually use newly approved drugs once they are marketed. The clinical trial experience may not perfectly reflect how the drug will be used in the health care system; therefore the true outcomes for patients may be unknown when physicians prescribe a drug.*²⁷

While it is true that no clinical trial can “perfectly reflect” the many ways in which a new drug may be used, the FDA is stretching its authority, and straining resources, in an attempt to regulate beyond its limited knowledge. The FDA is not bound by any statutory obligation to consider potential off-label use of drugs when determining safety and effectiveness. As such, the Agency should not predicate pre-market regulatory approvals on hypothetical use-cases not prescribed by a drug’s intended use.

Rather than hypothesize about potential off-label uses, the FDA should limit its consideration of a drug’s safety based on intended, label-specific use. Attempts at surmising a drug’s clinical utility in the doctor-patient context should be beyond the purview of any finalized benefit-risk assessment framework. This is especially true given the inherent difficulties such an approach presents to regulators. As the Draft PDUFA V Implementation Plan discusses:

[v]ariations in clinical and scientific judgments among FDA experts can lead to differing individual opinions and conclusions regarding the benefit-risk assessment. For example,

²⁵ “Guidance for Industry: Responding to Unsolicited Requests for Off-Label Information About Prescription Drugs and Medical Devices,” U.S. Department of Health and Human Services, Food and Drug Administration, December 2011, <https://www.fda.gov/downloads/drugs/guidances/ucm285145.pdf>.

²⁶ Draft PDUFA V Implementation Plan, p. 6.

²⁷ *Ibid.*, p. 2.

*while two experts may agree on a set of facts regarding the benefits and risks of a drug, the experts may not agree on accepting the risks given the demonstrated benefits of the drug. ... One expert might consider it worthwhile having the alternative available; the other might not agree unless the drug could be shown to work where others had failed. The decision on what to do would obviously depend on the nature and severity of the specific toxicity, how often available treatments fail, the severity of the condition being treated, and many other factors. Reconciling such differences and understanding where tradeoffs are made can be a challenging task for a regulator.*²⁸

This challenge is precisely why such decisions are better made at the doctor-patient level and why considerations of clinical utility and potential off-label use effects should be confined to the post-market surveillance setting. The post-market approval setting, therefore, is where the structured benefit-risk assessment can be most effectively leveraged in meeting the statutory requirements under the FDASIA amendment.

Limitations of Benefit-Risk Assessments in the Pre-Market Approval Phase

The Draft PDUFA V Implementation Plan acknowledges the “nuanced and conditional” nature of benefit-risk assessments, which leads the FDA to conclude “that the best presentation of benefit-risk considerations involves focusing on the individual benefits and risks, their frequency, and weighing them appropriately.”²⁹ For this reason, it is more appropriate for the FDA to confine its structured benefit-risk assessment approach to the post-market approval environment, in which doctors and patients can effectively communicate the real-world “individual benefits and risks” of approved drugs.

In addition, because the FDA considers hypothetical off-label uses and empirically-uncertain standards in determinations of drug safety, using the benefit-risk assessment framework in the pre-market approval stage is more likely to run counter to the intended purpose of the program—that is, it will not “improve the efficiency and effectiveness of the first cycle review process and decrease the number of review cycles necessary for approval, ensuring that patients have timely access to safe, effective, and high quality new drugs and biologics.”³⁰

As noted previously, the wide variation in individual biological responses to drugs makes guessing at “life outcomes” and clinical utility before a drug has even made it to the doctor-patient marketplace inadvisable. Such an approach runs counter to the purported focus on benefits and risks for individuals. A 2016 Mercatus study aptly summarizes this problem:

While clinical trials can show whether a drug is active in modulating disease parameters ... even the largest trials cannot control for the myriad factors that affect ultimate outcomes. In other words, choosing to base FDA decisions on benefits and risks implies

²⁸ Ibid., p. 3.

²⁹ Draft PDUFA V Implementation Plan, p. 4.

³⁰ PDUFA Reauthorization Performance Goals and Procedures, p. 6.

*that the FDA will take on the decision roles of physicians and patients, attempting to anticipate or predict their future choices.*³¹

Such assessments, the authors note, “can and should be analysed post-approval, in the medical marketplace.”³²

Recommendations

While the incorporation of the structured benefit-risk assessment framework into existing workflows and regulatory decision-making is by itself unobjectionable, fundamental problems in the regulatory approval process remain unaddressed. The Draft PDUFA V Implementation Plan, as currently constructed, does little to illuminate the rationale of the drug regulatory approval process, running contrary to the stated intent of FDASIA and the implementation goals of the benefit-risk assessment framework. In order to better reconcile the FDA’s statutory obligations under FDASIA with the current benefit-risk framework, the Agency should consider the following recommendations.

1. Narrow Pre-Market Approval Standards to Safety and Effectiveness

The FDA should better clarify the *specific* standards by which it assesses both “safety” and “effectiveness.” Such definitions should be clear, delimited to reasonable and objective metrics, and narrowed to the intended, labeled use of a new drug.³³ Safety and effectiveness should not be defined by outcomes-focused clinical trials that attempt to validate “life outcomes” or clinical utility. Rather, the FDA’s standards should examine more near-term and readily identifiable effects of a drug’s biological activity.

Further, the FDA should refrain from considering hypothetical off-label use or clinical utility of new drug applications. Neither is reliably discernible based on clinical trial data alone. In a world where digital technologies significantly condense the information feedback loops between patients, doctors, and institutions, a pre-market approval system that is contingent on speculating about off-label use is anachronistic and counterproductive to the FDA’s mission of promoting health.³⁴

³¹ Gulfo, Briggeman, and Roberts, “The Proper Role of the FDA,” p. 13.

³² *Ibid.*, p. 13.

³³ See Gulfo, Briggeman, and Roberts, “The Proper Role of the FDA,” p. 29 (“Define safety with regard to the likelihood of causing death, debilitation, or severe harm. ... Define effectiveness as having positive activity on the disease (amelioration or reduction of signs and symptoms, surrogate endpoints, biomarkers, etc.)”); See also Gulfo and Briggeman, “Fostering Resilience,” pp. 21-22. (“A drug’s approved label should contain the measures used to determine effectiveness, and the approved claims should be limited to the specific findings. There should be an explicit list of acceptable measures of effectiveness that can support approval, including pharmacodynamics effects on disease parameters, clinical signs and symptoms, biomarkers, surrogate endpoints, patient-reported data, comparative effectiveness, clinical outcomes, and survival. And there should be a strong caveat that those last three measures ... are not *necessary* to demonstrate effectiveness.”)

³⁴ Joseph A. DiMasi, PhD, Christopher-Paul Milne, DVM, MPH, JD, and Alex Tabarrok, PhD, “An FDA Report Card: Wide Variance in Performance Found Among Agency’s Drug Review Divisions,” *Manhattan Institute*, Project FDA Report, No. 7, April 2014, p. 5, https://www.manhattan-institute.org/pdf/fda_07.pdf. (“Safe and effective for the

Rather than evaluating off-label use *ex ante* during clinical trial phases, digital technology can be leveraged to use patient-reported outcomes as a new stream of evidence to evaluate off-label safety and effectiveness.³⁵

2. Apply a Tiered Order of Effectiveness Model to the Pre-Market Approval Process

In addition to narrowing and clearly defining the standards for “safe” and “effective,” the FDA should examine the possibility of establishing tiered categories of approval for new drugs. By establishing tiers of approval, based on objective and measurable standards, the FDA would open the floodgates for innovation in new drugs while improving the efficiency of the approval pipeline.³⁶

Such an approach, as outlined by Dr. Joseph Gulfo and Jason Briggeman, Ph.D.:

*would provide clear and unambiguous regulatory pathways to approval without undermining the FDA’s authority to adjudicate safety and effectiveness. It is also straightforward: Language in the claim itself would clearly communicate to physicians the most important information about the drug and the effect that physicians can expect from its use. To that end, our system should provide improved transparency and clarity in the approval process and more comprehensible communication to physicians and patients.*³⁷

A recent report from the President’s Council of Advisors on Science and Technology offered a similar recommendation. The report suggested that the FDA should “explore ways, within existing drug

American population as a whole is no longer the relevant paradigm; instead, the standard must shift to safe and effective *when physicians are targeting treatments based on deep, contextual knowledge of patients and diseases that is continually evolving*. In a world with molecular medicine and mass heterogeneity, the FDA’s role will change from the *yes/no* single rule that fits no one perfectly, to being a certifier of biochemical pathways and prescribing modalities that evolve with rapid feedback and scientific advances.”)

³⁵ Jeana Frost, PhD, Sally Okun, RN, Timothy Vaughan, PhD, James Heywood, BS, and Paul Wicks, PhD, “Patient-reported Outcomes as a Source of Evidence in Off-Label Prescribing: Analysis of Data From PatientsLikeMe,” *Journal of Medical Internet Research*, Volume 13(1), January 21, 2011, <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3221356/>. (“One advantage of collecting treatment information through an online community is the ability to reach a large population of users at relatively little marginal cost. As the Internet becomes more accessible, an increasingly diverse population is online and joining online communities for support with health problems. By gathering experiences directly from patients, researchers can elicit new types of data not recorded systematically through routine clinical practice, and which would be unlikely to attract funding for traditional clinical trials.”)

³⁶ One approach to category-based approvals has been offered by Dr. Joseph Gulfo and involves a four-tiered approach in which new drug applications are reviewed for approval based on the nature of evidence that would be used to support a sponsor’s claim of effectiveness. See Gulfo and Briggeman, “Fostering Resilience,” p. 23; See also “Tiered Order of FDA Approval Based on Evidence and of Effectiveness,” Fairleigh Dickinson University, Initiative for Patient-Centered Innovation, Report #10, November 2016, <http://www.josephgulfo.com/wp-content/uploads/2016/11/161120-Categories-of-approval-MI3.pdf>.

³⁷ Gulfo and Briggeman, “Fostering Resilience,” p. 28.

approval pathways, to carry out pilot projects to explore approaches for adaptive approval.”³⁸ An “adaptive approval” approach, the report noted,

*would involve a series of approval stages that would iteratively expand the market for a drug based on the evidence generated about the drug’s risks and benefits. Adaptive approval contrasts with the binary approach to drug approval that predominates today, whereby a drug is approved or rejected based on a given data package at a single moment in time; the binary approach fails to adequately acknowledge and signal evolving knowledge about risks and benefits.*³⁹

Although this recommendation stopped short of advocating for a “progressive” or tiered approval process enshrined in legislation, it nonetheless argued that the FDA should “undertake pilot projects within existing approval pathways.”⁴⁰ A simplified and streamlined approval process, under which clear definitions of safety and effectiveness can be measured, would greatly enhance the ability for the FDA to communicate the benefits and risks of new drugs while establishing a “consistent and systematic approach,” thus complying with the statutory requirements under the FDASIA amendment.

Conclusion

The goals of the structured benefit-risk assessment plan, as described under FDASIA, are laudable, and we wholeheartedly embrace the FDA’s focus on upgrading its IT infrastructure to promote electronic streamlining of new drug applications. Unfortunately, the PDUFA V Implementation Plan ignores the more fundamental problems that may complicate effectively communicating the benefits and risks of new drugs. Until and unless the FDA corrects the problems inherent in the pre-market clinical trial approval process, it is difficult to imagine how the Agency plans to abide by the statutory obligations imposed on it under FDASIA.

Luckily, the FDA’s organic statute already grants it the flexible authority necessary to make these changes. The Agency should use those powers to establish clear and unambiguous standards for “safe” and “effective” drugs, as well as address the other underlying problems in the pre-market approval process. Indeed, when even current FDA directors “believe the clinical trial system” is broken,⁴¹ it suggests the time for these types of reform are long overdue.

We would like to thank the FDA for the opportunity to comment on this issue and look forward to continued engagement on this and other topics.

³⁸ “Report to the President on Propelling Innovation in Drug Discovery, Development, and Evaluation,” Executive Office of the President, President’s Council of Advisors on Science and Technology, September 2017, p. 66, <https://obamawhitehouse.archives.gov/sites/default/files/microsites/ostp/pcast-fda-final.pdf>.

³⁹ Ibid., p. 65.

⁴⁰ Ibid., p. 67.

⁴¹ Zachary Brennan, “FDA’s Janet Woodcock: the clinical trials system is ‘broken’,” *Endpoints News*, September 20, 2017, <https://endpts.com/fdas-janet-woodcock-the-clinical-trials-system-is-broken/>.