COMMENTS OF THE COMPETITIVE ENTERPRISE INSTITUTE REGARDING FDA'S PROPOSED RECOMMENDATIONS FOR PRESCRIPTION DRUG USER FEE ACT REAUTHORIZATION

Docket No. FDA-2010-N-0128, 76 Fed. Reg. 56201 (September 12, 2011)

The Competitive Enterprise Institute (CEI) appreciates the opportunity to submit these comments regarding the FDA's proposed recommendations for reauthorization of the Prescription Drug User Fee Act. CEI is a non-profit research and advocacy organization that studies the impact of regulation on the economy, public health and welfare, and consumer choice. For the past 25 years, CEI has been extensively involved in issues related to drug, biologics, and medical device regulation, medical product labeling, and other public health and consumer protection issues.

The Prescription Drug User Fee Act has helped patients by ensuring that the FDA has greater resources available to review New Drug Applications and Biologics License Applications, and in turn ensuring that the agency is capable of providing more timely access to new medicines. Prior to enactment of PDUFA in 1992, median NDA review times for standard submissions often exceeded two years, giving rise to a scenario in which new medicines were frequently available to patients in other industrialized countries a full year or more earlier than to patients in the United States. After 1992, median review times for standard submissions were halved, and priority submissions are now typically reviewed in as little as six months.[1]

The health benefits of speedier approval decisions have been remarkable. One seminal study examined at all 662 drugs approved by the FDA from 1979 to 2002, as well as all drugs withdrawn from the market during that period. It concluded that the faster pace of approvals beginning in the 1990s benefited patients with an extra 180,000 to 310,000 years of life.[2] Although some FDA critics have argued that the agency now spends too little time reviewing NDAs and BLAs, there is no evidence that speedier reviews have decreased patient safety, or that longer reviews would improve the agency's capacity to identify patient hazards prior to approval.

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[1] Food and Drug Administration, "Trends in NDA and BLA Submissions and Approval Times," http://www.fda.gov/AboutFDA/ReportsManualsForms/Reports/UserFeeReports/PerformanceReports/PDUFA/ucm209349.htm.

[2] E.R. Berndt, A.H.B. Gottschalk, T.J. Philipson, and M.W. Strobeck, "Industry Funding of the FDA: Effects of PDUFA on Approval Times and Withdrawal Rates," *Nature Reviews Drug Discovery*, Vol. 4, No. 7 (July 2005), pp. 545-554.

The primary safety limitations associated with FDA reviews lay, not with reviewers being rushed to make approval or disapproval decisions, but rather with the inability of clinical trials to reveal a product's benefit/risk profile fully. Some risks and benefits can only be revealed after marketing approval is granted and the products are used by large patient populations. Dragging out the review of a new drug or biologic is therefore unlikely to improve patient health. Indeed, the rate of drug approval withdrawals remained essentially unchanged from the pre-PDUFA to post-PDUFA eras, despite rising and falling approval times during that period,[3] indicating that PDUFA has not resulted in greater risk to patients.

But, while PDUFA has successfully enabled FDA to provide a speedier approval process, there remain numerous shortcomings in agency oversight of drug and biologics development and marketing. Among these are increasing burdens being heaped on manufacturers during the clinical trial phases of drug development, a lack of communication and transparency between FDA and manufacturers both before and during the NDA and BLA review process, and a potent political environment that incentivizes FDA to resolve issues related to the heterogeneity of risks and benefits within patient pools by denying approval.

CEI is therefore pleased to see that the FDA's proposed recommendations for PDUFA reauthorization include several items that could begin to address these concerns. Among these are the agency's proposals to explore more formalized and transparent tools for weighing the risks and benefits of new medicines and a commitment to use patient-reported outcome measures in assessing risks and benefits.

Enhancing Benefit-Risk Assessment

Under the Food, Drug and Cosmetic Act, the FDA is tasked with ensuring that new drugs and biologics are safe and effective. But no medicines are perfectly "safe," in the sense that they have no potentially negative side effects. For many products, including drugs and biologics that treat serious life-threatening or disabling diseases, medicines may be considered safe enough, even in the presence of substantial known risks. What matters is that the expected benefits outweigh the expected harms.

The net effects of a medicine are not always well characterized, however. Drugs and biologics are generally tested in only a few thousand patients, leaving much unknown at the time an approval or disapproval decision must be made. The full benefit-risk profile of medicines is also not fully known even after they have been marketed for many years and used by hundreds of thousands or millions of patients. In practice then, the FDA must make a judgment about whether the potential benefits of new medicines outweigh their potential risks.

[3] Michael A. Friedman, Janet Woodcock, Murray M. Lumpkin, et al., "The Safety of Newly Approved Medicines: Do Recent Market Removals Mean There Is a Problem?" *Journal of the American Medical Association*, Vol. 281, No. 18 (May 12, 1999), pp. 1728-34.

The FDA's current process for assessing and balancing the benefits and risks of medicines is largely ad hoc, informal, and qualitative, however, relying primarily on the intuitive judgment of the agency's medical review staff and expert advisory committees.[4] As a 2007 Institute of Medicine (IOM) report indicated, more standardized and robust analysis of risks and benefits could improve agency decision-making with attendant improvements for public health.[5] The IOM report recommended that the agency "develop and continually improve a systematic approach to risk-benefit analysis for use throughout the FDA in the pre-approval and post-approval settings."[6]

In response to the IOM's recommendation, the FDA announced in April 2010 that it would introduce a five-item, mostly qualitative, risk-benefit grid that would consider the seriousness of the condition to be treated, the availability of alternative treatments, clinical data on the risks and benefits associated with a new drug's use, and relevant risk management practices associated with the product.[7] The purpose, according to Office of New Drugs Director John Jenkins, was to provide a template that would help the agency "visualize these risk-benefit decisions" that the agency already makes, while addressing "the critical issues that go into decision-making," and "transparently represent[ing] how decisions were made."[8]

The FDA's adoption of this risk-benefit grid was an important first step forward in improving the transparency and predictability of agency decision-making. However, implementation of a more formalized and comprehensive benefit-risk framework would do even more to promote those important goals. More formalized benefit-risk analysis is not a panacea. But implementing improved processes would help manufacturers better understand the kinds of data that must be generated during pre-clinical and clinical testing, help FDA product reviewers better systematize their decision-making, and help patients and medical clinicians better assess the utility of new products when prescribing treatment regimens.

Because clinical trials must, by necessity, be conducted with a limited number of patients and over a relatively short time period, assessing a drug's benefits and risks is challenging at best. And changes in many symptoms, such as pain and cognitive or motor skills impairment, necessarily rely on qualitative reports on the individualized experience of patients, which makes quantification and cross-comparison difficult if not impossible. Similarly, because the value of particular symptomatic improvements and a tolerance for risk vary among patients, the balancing of benefits and risks must necessarily entail subjective judgments.

Although the quantitative assessment of benefits and risks will always suffer from inadequacies, making greater use of quantitative assessments will nevertheless lead to an

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[4] *See*, Institute of Medicine, *The Future of Drug Safety: Promoting and Protecting the Health of the Public* (Washington, D.C.: National Academies Press, 2007), p. 123.
[5] Ibid.
[6] Ibid.
[7] Cole Werble, "FDA 'Grids' for More Transparent Risk-Benefit Decisions," *The RPM Report*, April 26, 2010.
[8] Ibid.

evaluation process that is more transparent, predictable, and rational. Properly conducted, benefit-risk analysis could help the FDA consider and compare all the relevant benefits and drawbacks of new medicines in a more systematic way, which would in turn contribute to greater treatment options and improved health outcomes.

Benefit-risk assessment – or, as it is known in other contexts, benefit-cost assessment – has a long history of use in regulatory decision-making. At its heart, benefit-risk analysis is nothing more than "a framework for taking diverse effects into account, including different forms of [risks] and benefits, effects occurring within different time frames, and varying degrees of uncertainty for potential effects."[9] It is an attempt to make possible the comparison of apples and oranges by reducing their characteristics to a common unit of measure. Particularly in cases that involve complex inter-related factors, such as drug and biologics approval decisions, benefit-risk analysis can help decision makers better understand the likely consequences of their actions.

Taking greater account of both sides of the benefit-risk equation is essential in making medical products approval decisions. Unnecessarily denying approval for a drug or biologic that is known to be risky, but which nevertheless has a positive benefit-risk balance could harm more patients than it would help – particularly when the product is intended to treat serious life-threatening or disabling conditions that have few other available treatment options. Indeed, while benefit-risk analysis and benefit-cost analysis have been criticized for inappropriately justifying decisions to place potentially risky products on the market, regulatory scholars John Graham and Jonathan Weiner propose that it be called "risk-risk assessment," because that framing best describes why the analysis is useful: Its ultimate goal is to identify which of many possible choices would lead to the best, or safest, overall outcome.[10]

It is, of course, true that not all effects, whether they are considered on the benefit or risk side of the equation, can be easily quantified. Still, even when certain values cannot be adequately expressed in quantitative terms, benefit-risk assessment calls for their existence, if not their measure, to be reflected in qualitative terms. Indeed, while benefit-risk assessment often takes a quantitative form, it would not be inappropriate to describe a purely qualitative comparison of benefits and risks as "benefit-risk assessment," so long as it is conducted in a thorough, careful, and searching manner.

Benefits and risks should be quantified when possible to enable comparisons across categories. Limitations in the chosen quantification methodology should be noted, as should plausible alternative quantification methods and the reasons for rejecting those measures. And the reasons for choosing any given qualitative measures should be explained. But qualitative factors will nevertheless be important considerations in most benefit-risk assessments.

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[9] Christopher M. Heimann, Daniel P. Bennett, Margaret C. Binzer, and Cameron N. Cosby, "The Impact of Cost-Benefit Analysis on Federal Administrative Law," *Administrative Law Review*, Vol. 42 (1990), p. 549.

[10] John D. Graham & Jonathan Baert Wiener, eds., *Risk vs. Risk: Tradeoffs in Protecting Health and the Environment* (Cambridge, Mass.: Harvard University Press, 1995).

In the end, benefit-risk assessment is not a dispositive tool that can make choices for agencies. Rather, it merely provides a framework for agency decision makers to "organize available information" by forcing them "to state their assumptions clearly, exposing possible biases to criticism and correction."[11] Therein lays another important feature of benefit-risk assessment in the drug and biologics approval process. Ultimately, the purpose of benefit-risk assessment is not to replace the judgment of medical experts in the decision-making process, but to put the FDA's expert judgments on record, explain the agency's reasons for approving or denying approval for new products, and hold those decisions up to public scrutiny.

Use of Patient-Reported Outcomes

Historically, patient views regarding the value of new treatment options have been given short shrift in the new drug and biologics approval process. For patients, medicines do more than simply treat or cure disease. They can produce uncomfortable, disabling, or embarrassing side-effects, but they can also improve patients' quality of life by reducing pain, discomfort, or other symptoms caused by the underlying medical condition. New or improved products can improve mental function or physical performance compared with alternative treatment options. And even a seemingly simple change in dosing frequency should not be discounted as trivial if it improves patient compliance with prescribed treatment protocols.

As the FDA explained in its *Federal Register* notice announcing these proposed recommendations, patient-reported outcomes (PROs) "are critical in understanding the drug benefits and harm from the patients' perspective."[12] CEI therefore applauds the FDA for recognizing the importance of patient perspectives, and we encourage the agency to vigorously incorporate PROs into the agency's drug and biologics evaluations – including in the more formalized benefit-risk assessments discussed above.

The FDA appropriately notes that "PROs require rigorous evaluation and statistical design and analysis to ensure reliability to support claims of clinical benefit."[13] However, it is important for the agency to consider the fact that patients' responses to medicines, and the values that patients place on quality of life improvements, are often highly heterogeneous. Patients will vary considerably in their tolerance for pain, discomfort, and other manifestations of their underlying disease conditions. They will also vary in their tolerance for the negative side-effects associated with the medications they use.

To the best of its ability, the FDA should not discount this inherent variability in patient responses and attitudes when designing or adopting statistical tools for assessing patient-reported outcomes. Patients are not all the same, and the realization that not all

[11] Heimann et al., "The Impact of Cost-Benefit Analysis on Federal Administrative Law," p. 551.
[12] Food and Drug Administration, "Prescription Drug User Fee Act; Public Meeting," *Federal Register*, Vol. 76, No. 176 (Sept. 12, 2011), p. 56,203.
[13] Ibid.

patient responses will fall neatly along the statistical median must be an integral component of PRO assessment. To the extent that statistical methods might inappropriately suggest that outlier responses are invalid or unimportant, the FDA would be jeopardizing the usefulness of PROs as a tool for improved drug and biologics evaluation. Even though statistical rigor is important, the agency should nevertheless take steps to include the full range of patient responses and attitudes in its decision-making process. And, where possible, the agency should take steps to make more products available for patient use, even though all patients may not be expected to experience the full range of potential benefits.

Conclusion

Again, CEI appreciates the opportunity to comment on the FDA's proposals for PDUFA reauthorization. We support the agency's efforts to introduce more rigorous and transparent benefit-risk assessment in the drug and biologics approval process and to take greater account of patient views regarding the value of the medicines they use.

The FDA already engages in risk-benefit balancing when considering NDA and BLA approvals. This new step would, however, make the process more transparent and predictable, and it would provide for more meaningful public oversight of FDA activities. Adopting a more formal and systematic benefit-risk assessment framework that includes patient-reported outcome measures will help manufacturers prepare improved NDA and BLA submissions, will help the agency weigh the significance of clinical data more systematically, and will help patients and clinicians better understand the risk-benefit profile of the treatment options they consider. Perhaps just as important, it will force the agency to lay bare its assumptions and valuations regarding the risks and benefits of new medicines in a way that will improve public understanding of agency decision-making and facilitate more robust public oversight.

Respectfully submitted,

Gregory Conko
Competitive Enterprise Institute
1899 L Street NW, 12th Floor
Washington, DC 20036
Phone: (202) 331-1010

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