
# Structured Approach to Benefit-Risk Assessment in Drug Regulatory Decision-Making

Draft PDUFA V Implementation Plan - February 2013

Fiscal Years 2013-2017

FDA

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## INTRODUCTION

FDA performs an essential public health task by ensuring that safe and effective human drugs and biological products are available to improve the health of the American people. To be approved for marketing, a drug must be safe and effective for its intended use. Although the meaning of "safe" is not explicitly defined in the statutes or regulations that govern approval, and recognizing that all drugs have some ability to cause adverse effects, the safety of a drug is assessed by determining whether its benefits outweigh its risks. This benefit-risk assessment is the basis of FDA's regulatory decisions in the pre-market and post-market review process. It takes into account the extensive evidence of safety and effectiveness submitted by a sponsor in a New Drug Application (NDA) or a Biologics License Application (BLA), as well as many other factors affecting the benefit-risk assessment, including the nature and severity of the condition the drug is intended to treat or prevent, the benefits and risks of other available therapies for the condition, and any risk management tools that might be necessary to ensure that the benefits of the drug outweigh its risks. This assessment involves both quantitative analyses and a subjective qualitative weighing of the evidence.

In the past, some FDA stakeholders have indicated that there is room for improvement in the clarity and transparency of FDA's benefit-risk assessment in human drug review. When FDA approves a new product, the agency publishes the various relevant documents, such as discipline reviews (e.g. clinical, non-clinical, clinical pharmacology, biostatistics, and chemistry) and decision memoranda, on its website. While FDA takes great care to clearly explain the reasoning behind a regulatory decision in these documents, the clinical analysis may not always be readily understood by a broad audience who may wish to understand FDA's thinking. In addition, some have argued that drug regulatory decisions should be based on more formalized and quantitative approaches to benefit-risk assessment, including the assignment of weights to benefit and risk considerations. Others, however, are skeptical of fully quantitative approaches, and consider such attempts to be a highly subjective exercise that would add little clarity to regulatory decision-making.

To address these concerns and enhance FDA's framework for benefit-risk assessment, the Agency began an initiative in 2009 to develop a structured approach for drug benefit-risk assessments that could serve as a template for product reviews, as well as a vehicle for explaining the basis for FDA's regulatory decisions in drug approvals. FDA's work in this area coincided with efforts elsewhere at other regulatory agencies, as well as in the regulated industry. When FDA and industry began discussions on reauthorization of the Prescription Drug User Fee Act (PDUFA) in 2010, an enhanced structured approach to benefit-risk assessment was a key topic. Those discussions resulted in a set of commitments during PDUFA V (FY 2013-2017) related to enhancing benefit-risk assessment in drug regulatory decision-making. These commitments can be found in the PDUFA V Performance Goals and Procedures document.

FDA's commitments include the publication of a draft five-year plan that describes the Agency's approach to further develop and implement structured benefit-risk assessment in the human drug and biological product review process. This document fulfills the PDUFA V commitment to publish the draft plan.[1] FDA will accept comment on this draft plan through a public docket. Throughout PDUFA V, FDA will update this document as necessary and publish all updates on the FDA website.

[1] On July 9, 2012, the President signed into law the Food and Drug Administration Safety and Innovation Act (FDASIA), (Public Law 112-144). Section 905 of FDASIA amends Section 505(d) of the Federal Food Drug and Cosmetic Act (FD&C Act) by requiring FDA to "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 decision-making, 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 premarket approval of a drug." The publication and implementation of this plan are intended to fulfill the requirement in Section 905 of FDASIA.

## BACKGROUND ON FDA'S FRAMEWORK FOR DRUG REGULATORY DECISION-MAKING

### 1 Drug Regulatory Decision-Making—At the Intersection of Law, Science, Medicine, Policy, and Judgment

Regulatory decisions that FDA makes in both the pre-market and post-market drug review process are based on the Agency's assessment of the benefits and risks of the product under review. This assessment is informed by science, medicine, policy, and judgment, in accordance with applicable legal and regulatory standards. The intersection of these components constitutes the framework in which FDA makes regulatory decisions. This framework begins with FDA's legal authority embodied in the Federal Food, Drug, and Cosmetic Act (the FD&C Act), the Public Health Service Act (PHS Act) and the regulations that the Agency issues to implement these Acts.

The law and regulations concerning the drug review process generally provide broad principles and are not case-specific, so the Agency works to develop consistent policy in taking action within its legal and regulatory authority. FDA communicates this policy through guidance and other policy documents, such as the Agency's extensive guidance on how to assess the effectiveness of drugs generally (e.g., when is one study sufficient, how should dose-response be assessed, what do we expect for demographic distribution, how to design non-inferiority studies, etc.) and guidance on development of specific classes of products. The Agency has also issued detailed guidance on how to assess both general and specific aspects of safety in the pre- and post-market setting. Guidances represent the Agency's current thinking on a topic and have general applicability. However, guidances are not binding and other approaches may be used as long as they comply with the governing statute and regulations. Indeed, FDA may in a given case determine that a generally applicable guidance is inappropriate, and in such cases retains the flexibility to adopt a different approach.

While the applicable law, regulations, and Agency policy provide the boundaries within which FDA makes regulatory decisions, the fields of science and medicine inform this process by providing a set of facts and the clinical judgment that permit an evaluation of a drug's effects on an intended patient population. Although science and medicine are distinct disciplines, they are increasingly converging as more is learned about human biology and disease. Drug regulation has played a crucial role in enabling this convergence. FDA requirements to study drugs using rigorous methods have yielded significant contributions to evidence-based medicine that reduce the uncertainty in terms of what benefit can be expected when a patient takes a drug. Applying the scientific method to understanding drug safety is often more challenging, because the signals of serious safety concerns are often quite small during pre-approval drug development. As such, the evaluation of drug safety often relies on post-market observational methods, and as a drug is used in greater numbers of patients and in more diverse populations, FDA's understanding of its safety profile improves in the post-market setting.

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. This is where social and behavioral science can inform regulatory decision-making. These areas of science consider cognitive and behavioral factors affecting human judgment and decision-making in the context of health care delivery. Methods from social and behavioral science are now being explored to support the development of more effective risk communication and risk management strategies for human drugs.

Despite the contributions of these disciplines to informing decision-making and providing greater insight in understanding and predicting real world behavior and outcomes, the available information

about a drug can be limited and may not address all of FDA's questions or concerns. This residual uncertainty creates the need for judgment in decision-making that is based on training and experience and allows regulators to determine whether a decision fits within the existing legal and policy framework, despite the uncertainty. Variations in clinical and scientific judgments among FDA experts can lead to differing individual opinions and conclusions regarding the benefit-risk assessment. For example, 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. While a new drug might be similar in effectiveness to available therapies, it may have an array of adverse effects that is different and to some degree worse than available therapies, e.g., if the adverse effects are more likely to lead to discontinuing therapy. 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.

Clearly the quantity of information that must be evaluated and considered by FDA is substantial, making the regulator's job very complex. A framework for benefit-risk decision-making that summarizes the relevant facts, uncertainties, and key areas of judgment, and clearly explains how these factors influence a regulatory decision, can greatly inform and clarify the regulatory discussion. Such a framework can provide transparency regarding the basis of conflicting recommendations made by different parties using the same information. When the final decision is made, a single framework provides a standardized, predictable, and accessible form that communicates the basis for FDA's regulatory decision to the public, while also documenting the decision for reference as FDA considers similar benefit-risk assessments in the future.

## 2 Development of a Benefit-Risk Framework

### 2.1 FDA's Approach to Developing a Benefit-Risk Framework

In 2009, FDA initiated an effort to explore more systematic approaches to benefit-risk assessment and communication as part of the human drug review process. This effort was driven first by the Center for Drug Evaluation and Research (CDER) leadership's desire to be clearer and more consistent in communicating the reasoning behind drug regulatory decisions, including which benefits and risks are considered, how the evidence is interpreted and what the implications of the evidence are for the benefit-risk assessment. Secondly, CDER also identified a need to ensure that reviewers' detailed assessments could be readily placed in the larger patient care and public health context.

FDA began with the recognition that certain principles were necessary for this effort to be relevant to reviewers and signatory authorities who make benefit-risk assessments on a daily basis. First, a benefit-risk assessment framework must operate within the applicable legal, regulatory, and policy framework for each regulatory decision. Second, a systematic approach to benefit-risk assessment should support the work of review staff throughout the lifecycle of a drug by capturing the full range of decisions from pre-market review through any regulatory actions that are necessary in the post-market setting. It should facilitate identification of the critical issues regarding benefit and risk and faithfully capture the review team's deliberation on those issues. The approach should also focus discussion and communication on the weighing of those issues, ensuring that benefit and risk considerations are kept in mind throughout review. Finally, a systematic approach should efficiently integrate into a review teams' existing processes and work products.

In the last few years, as other disciplines such as decision science and health economics have been applied to drug regulatory decision-making, there has been much discussion among regulators, industry, and other stakeholders regarding "qualitative" versus "quantitative" approaches to benefit-risk assessment. The term "quantitative benefit-risk assessment" can have various meanings depending on who is asked. Some hold the view that a quantitative benefit-risk assessment encompasses approaches that seek to quantify benefits and risks, as well as the weight that is placed on each of the components such that the entire benefit-risk assessment is quantitative. This approach is typical of quantitative decision modeling. It usually requires assigning numerical weights to benefit and risk considerations in a process involving numerous judgments that are at best debatable and at worst arbitrary. The subjective judgments and assumptions that would inevitably be embodied in such quantitative decision modeling would be much less transparent, if not obscured, to those who wish to understand a regulator's thinking. Furthermore, application of quantitative decision modeling seems most appropriate for decisions that are largely binary. Many benefit-risk assessments are more nuanced and conditional based on parameters that could be used to effectively manage a safety concern in the post-market setting. There is significant concern that reliance on a relatively complex model would obscure rather than elucidate a regulator's thinking.

These concerns have led FDA to the conclusion that the best presentation of benefit-risk considerations involves focusing on the individual benefits and risks, their frequency, and weighing them appropriately. FDA believes that this can be accomplished by a qualitative descriptive approach for structuring the benefit-risk assessment that satisfies the principles outlined earlier in this section, while acknowledging that quantification of certain components of the benefit-risk assessment is an important part of the process to support decision-making. FDA considers it most important to be clear about what was considered in the decision, to be as quantitative as possible in characterizing that information, and to fully describe how that information was weighed in arriving at a conclusion. Quantitative assessments certainly underpin the qualitative judgments of FDA's regulatory decisions, but FDA has adopted a structured qualitative approach that is designed to support the identification and communication of the key considerations in FDA's benefit-risk assessment and how that information led to the regulatory decision.

FDA's work in structured benefit-risk assessment coincided with efforts elsewhere in industry[2] and at other regulatory agencies, such as the European Medicines Agency (EMA)[3]. These approaches are quite similar in their most basic forms: defining the context in which the decision is being made, identifying the important relevant information and data regarding benefit and risk, assessing that information with respect to its bearing on the decision, drawing conclusions from the information based on expert judgment, and communicating the decision and its rationale. FDA's structured approach to benefit-risk assessment is described in more detail in the sections that follow.

### 2.2 Initial Work (FY 2009-2011)

When FDA began work to develop a formal benefit-risk framework, our first task was to study past drug regulatory decisions to characterize the general approach and structure for benefit-risk assessments that is already present in our decision-making, although perhaps not explicitly stated. We sought to develop a structure that faithfully represents the Agency's thought process and how we weigh the information when we make regulatory decisions. This work initially focused on decisions within CDER

[2] Coplan, PM, Noel RA, Levitan BS, Ferguson J and Mussen, F (2011). Development of a Framework for Enhancing the Transparency, Reproducibility and Communication of the Benefit–Risk Balance of Medicines. *Clinical Pharmacology & Therapeutics*, 89(2): 312–315.

[3] See European Medicines Agency (2012). Benefit-risk methodology project. Accessed 11/30/2012 at http://www.ema.europa.eu/ema/index.jsp?curl=pages/special_topics/document_listing/document_listing_000314.jsp&mid=WC0b01ac0580223ed6

and was supported by decision science and drug regulatory expertise provided by IMS Government Solutions, as well as an advisory group of senior management in CDER that included representatives of the Office of New Drugs, the Office of Surveillance and Epidemiology, and the Office of Biostatistics. We focused on prior cases that represented relatively challenging benefit-risk assessments. The rationale for this approach was that where a regulatory decision is complex and not straightforward, clearly communicating the reasoning behind the decision to all audiences is particularly important. These cases also represented the range of regulatory decisions that are made by CDER, including approval, non-approval, and post-marketing actions.[4] We recognized that a framework must be able to handle challenging benefit-risk decisions at any point in a drug's lifecycle.

As part of this work, we interviewed each review discipline that had a role in the particular regulatory decision, as well as the Office of New Drugs review division and office management where the decision authority resided. In these discussions, we sought to understand the important benefit-risk considerations that weighed on the regulatory recommendation and decision. This analysis showed that review considerations could be appropriately grouped in several areas. These considerations included the necessary information about the demonstrated benefits and risks of the proposed drug identified through careful review of the submitted clinical data. Risk management considerations, including recommended labeling language, represented another key consideration if review staff felt these were needed to manage important safety concerns. In reviewing our prior decisions, we recognized that consideration was also given to information about the disease to be treated or prevented and the benefits and risks of other available therapies for the disease. This information provides the context for the regulatory decision that has an important impact on how a regulator thinks about the benefit-risk assessment of a drug. For example, consideration of the context of the decision was evident in CDER's decision to approve an application to resume marketing of Tysabri, subject to a restricted distribution program. Originally approved in 2004 for relapsing forms of multiple sclerosis (MS), Tysabri was withdrawn from the market by the manufacturer in 2005 after the drug was linked with progressive multifocal leukoencephalopathy (PML), a rare, frequently fatal neurological condition. In reviewing a restricted distribution plan to manage the risk of PML as well as additional efficacy data, in 2006, CDER convened an advisory committee meeting on remarketing Tysabri. At the meeting, patients, family members, and health care providers testified to the difference that Tysabri had made in the lives of MS patients, as well as the willingness of patients to continue treatment despite the risk of PML. This testimony and the unanimous AC recommendation to return Tysabri to the market indicated that, despite other available therapy options for MS, there was still an unmet medical need in this progressively debilitating inflammatory neurological disease that was filled by Tysabri, a more effective drug than other available therapies. FDA ultimately determined that the serious risks associated with this drug were acceptable, because they were outweighed by the benefit of the drug to patients. Although Tysabri's greater effect in a very debilitating disease is a particularly striking example, there are often advantages and disadvantages of available therapies that would be considered in decisions about new drugs.

From this analysis of prior regulatory decisions, we developed a basic structure of a benefit-risk framework that includes the following categorization of key decision factors: Analysis of Condition, Current Treatment Options, Benefit, Risk, and Risk Management, where:

- *Analysis of Condition* and *Current Treatment Options* provide a summary and assessment of the severity of the condition that the product is intended to treat and other therapies available to

[4] As some of the information related to these cases is not public information, they are not discussed in this document.

treat the condition. This represents the context of the decision that can provide useful information for weighing the benefits and risks of the drug under review.

- *Benefit* and *Risk* provide a summary and assessment of the submitted evidence concerning the drug under review. Key considerations of benefit include the results of the clinical trials and the clinical meaning of primary and secondary endpoints, as well as appropriate analyses of subpopulations. Key considerations of risk include the adequacy of the safety database, the severity and reversibility of adverse events, and the potential for sub-optimal management in the post-market setting that may be of concern. In assessing benefit and risk, consideration is also given to other factors that may be relevant for a particular drug review, including non-clinical pharmacology and toxicology data; clinical pharmacology (e.g., mechanism of action, pharmacodynamics, and pharmacokinetics); chemistry, manufacturing, and controls (CMC); and clinical microbiology.
- *Risk Management* provides a summary and assessment of any efforts that could help to mitigate the identified safety concerns, or ensure that the drug is directed to those patients for whom the risk is considered acceptable.

Within each of these factors, there are two considerations that inform the regulatory decision. The first consideration consists of identifying facts as well as uncertainties and any assumptions that need to be made to deal with what is not known. The second consideration consists of the conclusions that must be made about each decision factor. These conclusions are the subjective interpretation of the evidence for each aspect of the benefit-risk assessment. We term these two categories as *Evidence and Uncertainties* and *Conclusions and Reasons*, where:

- *Evidence and Uncertainties* presents the facts, uncertainties, and any assumptions made to address these uncertainties that contribute to the assessment of benefit and risk.
- *Conclusions and Reasons* captures the implications of the facts, uncertainties, and assumptions with respect to regulatory decision-making, drawing conclusions from the evidence and uncertainties and explaining the bases for those conclusions.

Figure 1 on the next page presents FDA's Benefit-Risk Framework. The first two decision factors, Analysis of Condition and Current Treatment Options, represent the framework's *therapeutic area* considerations and are distinct from the other drug-specific considerations in the framework. The therapeutic area information represents the current state of knowledge regarding the condition and the available therapies and can be completed for any disease area. As the available therapies for a disease area change or as knowledge and understanding of the disease improves, this information can be updated.

**Figure 1: FDA Benefit-Risk Framework**

| Decision Factor | Evidence and Uncertainties | Conclusions and Reasons |
|---|---|---|
| Analysis of Condition | | |
| Current Treatment Options | | |
| Benefit | | |
| Risk | | |
| Risk Management | | |
| **Benefit-Risk Summary Assessment** | | |

The additional factors of Benefit, Risk, and Risk Management represent the *product-specific area* of the framework. The information found here relates specifically to the drug under review. As our knowledge of a drug's benefits and risks changes post-approval, this information can be updated in the framework, reflecting the dynamic nature of benefit-risk assessment during the drug lifecycle.

The final row of the framework is the *Benefit-Risk Summary Assessment*, a succinct well-reasoned summary that clearly explains FDA's rationale for the regulatory action including important clinical judgments that contributed to the decision. The summary should integrate the analyses of benefit and risk and the applicable statutory and regulatory standards into a coherent explanation of the conclusions reached. The assessment draws on the key supporting evidence and uncertainties, accounts for the understanding of the condition, and considers the available therapies that establish the context in which benefits and risks are weighed. It also includes the rationale to support the labeling and other risk management as well as post-marketing requirements/commitments if more information is necessary to further characterize the benefits or risks of the drug. Where there are differences of opinion within a review team with respect to scientific or clinical judgment, they are noted in the assessment along with an explanation of how the differences were resolved or taken into account in the final decision.

### 2.3 Pilot Project (FY 2012)

Since the framework was developed using retrospective case studies, the next step involved piloting the framework in the drug review process using applications under review in CDER. This effort began in FY 2012 using six new molecular entity (NME) NDAs or BLAs with the purpose of devising and testing a potential implementation approach that asked review teams to begin identifying the important benefit and risk considerations in the framework at the mid-point of the review process. As the review progressed the framework was refined to reflect, for example, any review issues that were resolved or new issues that emerged.

The frameworks developed as case studies for past regulatory decisions served as a guide for the kind of information that reviewers were expected to include in a framework. Additional points for reviewers to consider were also provided within each cell of the framework structure using question-based prompts to direct reviewers' completion of the framework. The prompts elicited the critical information that was considered as part of CDER's evaluation of the application under review.

The outcome of this pilot provided valuable insight from review staff and signatory authorities in terms of informing the future implementation of the benefit-risk framework in drug review. Overall, review staff and signatory authorities felt that the framework's structure successfully represented the key considerations of their benefit-risk assessment in a concise format. Reviewer feedback also led to improvements in the framework prompts to ensure that review considerations from multiple disciplines were adequately represented. In addition, other comments from review staff and signatory authorities suggested a potential implementation approach that would have the primary clinical reviewer creating a draft of the benefit-risk assessment framework as part of their review. The draft framework would be further refined by the Cross-Discipline Team Leader (CDTL) in CDER's 21st Century Review Process to incorporate input from other disciplines. After CDTL review, the benefit-risk framework would be reviewed and finalized by the signatory authority as part of the review of the action package. With the expanded implementation of the framework in PDUFA V, additional experience may suggest modifications to this potential implementation strategy.

An important concern expressed by review staff was that the benefit-risk framework had to be integrated into the existing work processes of review staff, rather than representing an added layer of effort. Accordingly, FDA is considering approaches to address this concern as an important part of our implementation planning effort in FY 2013 (see Section 3.1).

## BENEFIT-RISK FRAMEWORK IMPLEMENTATION IN PDUFA V

### 3 FY 2013—Further Development of the Framework

#### 3.1 CDER and CBER Clinical Review Templates and Decision Memoranda

FDA's PDUFA V commitments include reference to revision of CDER's Clinical Review Template, the Office and Division Director Summary Memoranda Templates, and equivalent Center for Biologic Evaluation and Research (CBER) documents to incorporate structured benefit-risk assessment in the human drug review process. As noted in Section 2.3 of this document, integrating the benefit-risk framework into reviewers' existing work was considered an important step by the review staff who participated in the pilot project. Therefore, prior to the staged implementation approach described in Section 4, CDER and CBER will work to address reviewer needs by developing clinical review templates that integrate the structured benefit-risk assessment offered by the framework, while preserving appropriate aspects of the current review templates. The goal of this work will be to produce a template that is user-friendly for review staff and generates work products that are valuable and informative to CDER and CBER leadership. A similar approach will be used in the integration of the benefit-risk framework into the summary memoranda that are written by review management in CDER and CBER.[5]

#### 3.2 Adaptation to Key Considerations in the Post-Market Setting

Once a drug is approved and marketed, we often gain additional information as the drug is used and studied in broader and more diverse populations. Sometimes this new information pertains to the benefit of the drug, particularly if health outcomes trials (e.g., those that identify cardiovascular benefits in lipid-altering drugs) are conducted after the drug is approved as is often the case. In many cases, the new information relates to the drug's safety. With this in mind, another important part of

[5] In CDER, review management generally refers to the Cross-Discipline Team Leader, the Division Director, and the Office Director in the offices within the Office of New Drugs. In CBER, review management generally refers to the Review Committee Chair/Scientific Lead and the Division Director or Office Director in the review offices.

the Agency's commitments in PDUFA V concerns enhancing and modernizing the FDA drug safety system. Several of these commitments pertain to our authority to require risk evaluation and mitigation strategies (REMS) to manage a known or potential serious risk associated with a prescription drug or biological product in the postapproval context. The FDA Amendments Act of 2007 granted FDA the authority to require REMS, if FDA becomes aware of new safety information and determines that such a strategy is necessary to ensure that the benefits of a drug outweigh its risks. In PDUFA V, we have committed to publishing a draft guidance on how to apply this statutory standard for determining whether a REMS is necessary to ensure that the benefits of a drug outweigh its risks. FDA has formed a working group to address our commitment to publishing the draft REMS guidance. Because the benefit-risk framework was developed with our postmarket risk management authority in mind, there is a link between the framework and this PDUFA V commitment, and we anticipate that the benefit-risk framework effort will inform development of the draft guidance.

As additional information is learned about the benefits and risks of drugs in the post-market setting, use of a framework in reviewing a drug's benefit-risk assessment can facilitate the balanced consideration of benefits and risks. When post-market considerations have been more fully incorporated into the benefit-risk framework, FDA intends to apply the framework to post-market review of a drug's benefit-risk assessment when new information becomes available.

### 3.3 Characterization of Uncertainties in Benefits and Risks

Although drug regulatory decisions are informed by an extensive body of evidence on the safety and efficacy of a proposed product, in many cases, FDA must draw conclusions from imperfect data. Therefore, identifying and evaluating sources of uncertainty (e.g., absence of information, conflicting findings, marginal results) is an important part of reviewers' work, and as we noted in Section 2.2, we have acknowledged the role of uncertainty in the benefit-risk framework. However, drawing conclusions in the face of uncertainty can be a complex and challenging task. Furthermore, being explicit about the impact of uncertainty on decision-making is an important part of communicating regulatory decisions. An approach that allows for more systematic accounting of the various sources of uncertainty and the role of uncertainty in decision-making can facilitate the characterization, integration, and communication of this information in drug review.

There are two areas where we intend to focus efforts beginning in FY 2013. The first is characterizing the uncertainty in how well the benefit-risk assessment based on pre-market clinical trial data translates to the post-market setting after the drug is approved and used in a much wider patient population. Clinical trials are designed to demonstrate a benefit of a drug compared to some comparator, such as placebo or another drug. During those trials, certain patients may be excluded to improve the ability to detect a benefit that can be attributed to the drug, or they may be excluded because of a potential safety concern. However, a clinical trial population with these exclusions may not be representative of the broader patient population that will ultimately take the drug in the post-market setting. Examples of potential differences include trial exclusions of patients on concomitant therapies, patients with other chronic conditions, or patients over a certain age. In other cases, the duration of the clinical trials may be different from the expected duration of use (e.g., antihypertensive drugs and antidiabetic drugs used chronically) or the quality and extent of patient monitoring may not be as rigorous in the post-approval setting as in the clinical trial (e.g., anticoagulants). Being clear about such differences, understanding their impact on decision-making, and adequately communicating these sources of uncertainty are very important.

The second area pertains to our level of uncertainty about a result or finding, particularly a new finding that becomes available in the post-market setting where the basis for the finding comes from sources

of varying levels of rigor. In contrast to the prospective and highly planned studies of effectiveness, safety findings emerge from a wide range of sources, including spontaneous adverse event reports, epidemiology studies, meta-analyses of controlled trials, or in some cases from randomized, controlled trials. However, even controlled trials, where the evidence of an effect is generally most persuasive, can sometimes provide contradictory and inconsistent findings on safety as the analyses are in many cases not planned and often reflect multiple testing. A systematic approach that specifies the sources of evidence, the strength of each piece of evidence, and draws conclusions that explain how the uncertainty weighed on the decision, can lead to more explicit communication of regulatory decisions. We anticipate that this work will continue beyond FY 2013.

## 4 FY 2014-2017—Implementation

FDA plans to use a staged approach in implementing the benefit-risk framework in human drug review. This allows opportunity for continued refinement of the framework and its integration into the human drug review process before further expansion into additional types of applications. During FY 2014 and 2015, FDA plans to implement the framework in the review of NME NDAs and original BLAs. As the benefit-risk assessment is revisited in the post-market setting based on new information for these applications, review teams analyzing the safety issue will be expected to update the benefit-risk framework with the analysis conducted, including any regulatory action resulting from that work, as appropriate. Following implementation in NME NDAs and original BLAs, FDA intends to implement the framework in efficacy supplements for new/expanded indications in FY 2016 and all original NDAs in FY 2017. The following table summarizes the implementation timeline:

| Application Group | Fiscal Year |
|---|---|
| New Molecular Entity New Drug Applications<br>Original Biologics License Applications | 2014-2015 |
| Efficacy Supplements for New/Expanded Indications | 2016 |
| All Original NDAs | 2017 |

## 5 Training and Communication

Following integration of the benefit-risk framework with the CDER and CBER clinical review templates and summary memoranda templates, training will be offered to reviewers and decision-makers in the use of these materials. Such training may entail face-to-face (just-in-time) training for the reviewers and decision-makers who will be expected to implement the framework, as well as an introduction to the benefit-risk framework as part of CDER and CBER's New Reviewer Training. Both Centers will also revise current procedural documents for staff and decision-makers that include revision of the Manual for Policies and Procedures that governs CDER's clinical review template and associated appendices as well as the Standard Operating Practices and Procedures document that governs CBER's clinical review template.

Current clinical reviews can be rather lengthy, highly detailed documents. Distilling such an extensive document down to a short and concise summary can be challenging and may also highlight the need for an additional type of training. Over time, CDER and CBER will build a database of worked examples of benefit-risk frameworks that can be used as a reference for reviewers. Such a database can serve a dual purpose of providing examples of high quality frameworks as well as establishing an easily

accessible set of regulatory precedents that can be a future reference when similar regulatory decisions must be made.

Following implementation of the benefit-risk framework in the drug review process, FDA intends to publish the completed frameworks for newly approved products on its website, to the extent that we are permitted to release the information under applicable disclosure laws. By the end of FY 2014, FDA anticipates posting benefit-risk frameworks of approved products following the regulatory action. Over this same time period, FDA also anticipates integrating the benefit-risk framework as part of Advisory Committee background packages to quickly orient the committee to the important review issues in the application under discussion.

## 6 Change Control Board

### 6.1 Purpose

Consistent with CDER and CBER's approach to continuous improvement, inevitably there will be a need to periodically review and modify the benefit-risk framework as well as the review templates and decision memoranda in each Center. These revisions could result from increased reviewer experience with the framework, feedback from Center management related to increasing the utility of the framework, and feedback from public stakeholders related to the framework's ability to communicate FDA's rationale for regulatory decisions. Because CDER and CBER are responsible for the regulation of different types of products, each Center plans to establish a Change Control Board (CCB) that will be responsible for analyzing feedback and input on the benefit-risk framework from their respective review staffs and making recommendations for enhancements to the framework and the clinical review templates for each Center. Although each Center will maintain some autonomy in terms of their respective clinical review templates, the CDER and CBER CCBs will ensure close coordination across the Centers on the harmonization of the benefit-risk framework structure as well as implementation of the framework in the review of human drugs and biological products.

### 6.2 Board Composition

A key source of feedback regarding recommended modifications to the benefit-risk framework will come from the review staff who use it during their review work. Accordingly, the CCBs in CDER and CBER will be composed of primary clinical review staff as well as review management from the Office of New Drugs in CDER or the review offices (Blood, Vaccines, and Cellular, Tissue, and Gene Therapies) in CBER, as appropriate. Because of the risk and risk management considerations in the framework, representation is also expected from CDER's Office of Surveillance and Epidemiology on the CDER CCB and from CBER's Office of Biostatistics and Epidemiology on the CBER CCB.

## 7 Benefit-Risk Advisory Group

### 7.1 Purpose

Each Center also intends to maintain an internal Benefit-Risk Advisory Group that will serve three purposes: (1) to provide overall direction in implementing structured benefit-risk assessment in the drug and biological product review process in each Center, (2) to evaluate finished benefit-risk frameworks and other work products to ensure consistent and high-quality representation of CDER and CBER decision-making before publication, and (3) to review and approve proposed modifications to the benefit-risk framework and the clinical review template that are recommended by the respective CCBs. The CDER and CBER Advisory Groups will ensure close coordination across the Centers regarding the harmonization of the benefit-risk framework structure as well as implementation of the framework in the review of human drugs and biological products.

### 7.2 Advisory Group Composition

The CDER Advisory Group is expected to be composed of the following leadership positions:

- Director, Office of New Drugs
- Director, Office of Surveillance and Epidemiology
- Director, Office of Medical Policy
- Deputy Director for Clinical Science
- Director, Office of Planning and Informatics

The CBER Advisory Group is expected to be composed of the following leadership positions:

- Associate Director for Medicine
- Associate Director for Review Management
- Associate Director for Policy
- Director, Office of Biostatistics and Epidemiology

## ADDITIONAL PDUFA V COMMITMENTS ON ENHANCING BENEFIT-RISK ASSESSMENT

### 8 Benefit-Risk Workshops in PDUFA V

As part of enhancing benefit-risk assessment in PDUFA V, FDA has committed to holding two public workshops on benefit-risk considerations from the regulator's perspective. The first workshop, slated to be held in early FY 2014, is expected to focus on the various frameworks and methods available and their appropriate application to drug regulatory decision-making. FDA anticipates that this workshop will include participation of other drug regulatory authorities who are also implementing benefit-risk frameworks in their drug decision processes. This discussion will examine the ability of frameworks to make explicit the benefit and risk considerations and associated uncertainties and assumptions that are part of drug regulatory decision-making.

The second workshop is expected to focus on the results of implementing frameworks at regulatory agencies both in pre-market application review as well as post-market safety review. This meeting will be an opportunity to share any challenges and lessons learned in applying a more structured approach to regulatory decision-making. As implementation progresses in PDUFA V, further detail regarding FDA's plan for this workshop will be included in an update to this document.

### 9 Evaluation of the Benefit-Risk Framework

The PDUFA V Commitments also require that this draft five-year plan include a plan to evaluate the impact of the benefit-risk framework in the human drug review process. The specifics of our implementation approach are still evolving as review staff acquire experience and provide feedback on the framework and its implementation in drug review. In addition, comments received on this draft plan from the public may suggest alternatives to our approach. Furthermore, as we integrate the framework concepts into our clinical review template during FY 2013, we expect that this experience will lead to best practices that will be applied to implementation of the framework in FY 2014. At that time, a more informed evaluation of the impact of the benefit-risk framework can be specified. FDA anticipates that this evaluation will consider the utility of the framework in communicating key benefit and risk considerations both internally and externally, facilitating decision-making including decisions about risk management, and training new review staff. Some of the evaluation questions we expect to examine include (1) whether the framework provides a clearer explanation of FDA approval decisions to public stakeholders, including patients, consumers, healthcare professionals, and industry; (2) whether

the framework provides value to internal reviewer communications and discussions related to pre-market regulatory decisions; and (3) whether the framework provides value in supporting consideration of emerging safety and efficacy information in post-market drug decision contexts. Given the implementation timetable described in Section 4, we expect that the evaluation will begin in FY 2015-2016 after full implementation has occurred in a sufficient number of application reviews. More information regarding the evaluation will be included in an update to this document.

## 10 Patient-Focused Drug Development

As described in Section 2.2, an analysis of the context of a regulatory decision is an important component of the benefit-risk assessment. These considerations are embodied by the Analysis of Condition and Current Treatment Options sections of the benefit-risk framework. FDA recognizes that patients have a unique and valuable perspective on these considerations and believes that drug development and FDA's review process could benefit from a more systematic and expansive approach to obtaining the patient perspective. Though several programs exist to facilitate patient representation, there are currently few venues in which the patient perspective is discussed outside of a specific product's marketing application review. In PDUFA V, FDA committed to a new initiative known as Patient-Focused Drug Development with the objective of obtaining the patient perspective on the condition and the currently available therapies for a set of disease areas during FY 2013-2017. For each disease area, FDA will conduct a public meeting and will invite participation from FDA review divisions, the relevant patient advocacy community, and other interested stakeholders. FDA began work on this initiative in Fall of 2012 by publishing a proposed list of disease areas and conducting a public meeting on October 25, 2012, during which patient advocates offered their input on FDA's proposal.[6] In early 2013, FDA anticipates publishing the set of disease areas that will be addressed during the first three years of PDUFA V. FDA will conduct a similar public process for determining the list of disease areas for FY 2016-2017.

[6] http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm326192.htm