



Biotechnology  
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# A LIFECYCLE APPROACH TO FDA'S STRUCTURED BENEFIT-RISK ASSESSMENT FRAMEWORK

This White Paper was developed by the Structured Benefit-Risk Working Group of the Biotechnology Industry Organization (BIO). The paper identifies considerations for biopharmaceutical companies who choose to use FDA's Structured Benefit-Risk Assessment Framework earlier and more broadly throughout a product's lifecycle as a mechanism to both solicit patient perspectives on areas of unmet medical need and assess patient preferences, and to align with FDA on key benefit-risk considerations.

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# CONTENTS

1. Executive Summary
2. Background
3. Use of the Structured Benefit-Risk Assessment Framework Earlier in Drug Development
4. Use of the Structured Benefit-Risk Assessment Framework during Drug Development, Review, and Post-Approval
  - A. Early Stage Development
  - B. Mid-to-Late Stage Clinical Development
  - C. NDA/BLA Submission
  - D. Late Cycle Meeting
  - E. Advisory Committee Meeting
  - F. FDA Approval
  - G. Post-Approval
5. Implementation Challenges
6. Conclusion

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## EXECUTIVE SUMMARY

By definition, drugs have both benefits and risks that must be carefully balanced in FDA's approval decisions. The fifth reauthorization of prescription drug user fees (PDUFA V) in the Food and Drug Administration Safety and Innovation Act (FDASIA) in 2012 represented a significant first step toward realizing a vision of patient-centric benefit-risk assessment. By establishing a structured framework for visualizing the comparative benefits and risks and incorporating it into FDA's review templates, FDA and sponsors can understand and communicate more effectively the judgments that went into an FDA product approval decision.

FDA is currently implementing a structured benefit-risk assessment framework (sB/R) to organize its review of a product's benefit and risk, and communicate benefit-risk assessment decisions at the point of approval or post-market regulatory decision. However, the sB/R framework is a powerful tool for not only standardizing a holistic assessment of benefits and risks, but for incorporating the patient perspective and guiding sponsor-FDA discussions and decisions throughout the drug development continuum.

This White Paper outlines a voluntary, private sector-led initiative for biopharmaceutical companies to use the sB/R framework earlier during the drug development process, offering key considerations and strategies to implement the framework in a more structured, systematic and proactive manner.

Under the process outlined in this paper, sponsors will be able to use the sB/R framework to better align on key benefit-risk considerations across the drug development lifecycle with both patients and FDA. Using the vocabulary of the sB/R framework, benefit-risk evaluation shifts to an iterative, evolving, and collaborative process among the sponsor, the Agency, and patients, with the aim of achieving a common understanding of benefit-risk in a patient-centric manner.

## BACKGROUND

A key element of the 2012 PDUFA V reauthorization and passage of FDASIA was the requirement for FDA to establish a structured benefit-risk framework to improve the transparency and clarity of FDA's benefit-risk decisions and to communicate more effectively the subjective value judgments underlying benefit-risk determinations. FDASIA directs 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."<sup>1</sup>

In February 2013, FDA released a draft 5-year plan, PDUFA V Implementation Plan: Structured Approach to Benefit-Risk Assessment in Drug Regulatory Decision-Making, which explains that fundamental to FDA's review of new products are a set of clinical judgments and facts regarding the balance of benefits, risks, unmet medical need, social and behavioral science, and scientific uncertainty:

*"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*

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<sup>1</sup> Federal Food, Drug and Cosmetic Act, §505(d)

considers similar benefit-risk assessments in the future.”<sup>2,3</sup>

The sB/R framework is characterized as a 5x3 grid that reviewers will fill-in with a lay-friendly description of key benefit-risk determinations, including an analysis of the condition, available treatment options, clinical benefits, risks, and potential approaches to minimize risk (Figure 1).

The first two domains of the framework, “Analysis of the Condition” and “Current Treatment Options,” are informed by incorporating patient views of their own condition and care. Feedback received during FDA’s Patient Focused Drug Development meetings is being used to help fill in these domains and is included in the “Voice of the Patient” reports that capture the meeting proceedings.

Figure 1: FDA’s Structured Benefit-Risk Framework:

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition		
Current Treatment Options		
Benefit		
Risk		
Risk Management		
<b>Benefit-Risk Summary Assessment</b>		

Over the last two years, FDA has been piloting the framework and integrating it into review templates and standard operating procedures used by all drug and biologics reviewers. Starting in 2015, FDA began using the framework as part of the new molecular entity (NME) review process and plans to expand its use to all new drug applications (NDAs)/biologics licensing application (BLAs), as well as in post-approval benefit-risk decisions. At this point, both the Agency and sponsors have limited experience with the framework, but the initial reception from reviewers and industry has been positive.

Figure 2: Structured Benefit-Risk Implementation Schedule:

<b>2012</b>	Pilot 6 NMEs, refine framework
<b>2015</b>	NMEs and Original BLAs
<b>2016</b>	Efficacy Supplements for New/Expanded Indications
<b>2017</b>	All Original NDAs

FDA will make public its sB/R analysis for approved drugs only; and there are no plans to release the analyses for drugs that are not approved, or prior to approval, due to confidentiality requirements. The extent to which or how the framework will be explicitly used in late cycle meetings, Advisory Committee meetings, or in labeling discussions with sponsors is unclear.

<sup>2</sup> FDA, Structured Approach to Benefit-Risk Assessment in Drug Regulatory Decision-Making, February 2013, [http://www.fda.gov/downloads/For\\_Industry/UserFees/PrescriptionDrugUserFee/UCM329758.pdf](http://www.fda.gov/downloads/For_Industry/UserFees/PrescriptionDrugUserFee/UCM329758.pdf)

<sup>3</sup> FDA, Benefit-Risk Considerations in CDER: Development of a Qualitative Framework, June 28, 2012, [http://www.fda.gov/downloads/About\\_FDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/UCM317788.pdf](http://www.fda.gov/downloads/About_FDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/UCM317788.pdf)

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# USE OF THE STRUCTURED BENEFIT-RISK ASSESSMENT FRAMEWORK EARLIER IN DRUG DEVELOPMENT

The sB/R framework is a tool for standardizing a holistic assessment of benefit and risk, and may provide more granularity to both physicians and patients when tailoring a particular intervention to a specific patient's needs.

Since the framework establishes the format and content for discussing benefit and risk, it could be helpful for sponsors to adopt the sB/R framework early in the development process, use consistently, and gradually align with FDA over the course of the development program.

This paper identifies key considerations for those companies that choose to make this a standard way to articulate benefit-risk and incorporate the patient's voice while gaining alignment with FDA by using a common vocabulary.

## A. Incorporation of the sB/R Framework as a Decision Tool

In response to the release of FDA's draft 5-year plan, BIO's 2013 comments<sup>4</sup> endorsed the notion of using the framework during drug development:

*"[A] common FDA-industry understanding of how benefit-risk will be assessed in a particular disease area. For instance, the framework could be utilized as a helpful FDA-sponsor communications tool as early as the end-of-phase 2 meeting. Further, the framework could be used as a tool in the same way that the Target Product Profile is used, and would not be considered a binding document, but could serve as a platform for discussion at appropriate meetings. Thus, the framework would serve as a commonly accepted decision-support tool for industry utilization, for example, to help inform a sponsor's decision to advance or discontinue a clinical development program."*

Much of the information available in the Investigator's Brochure should be directly transferable to the sB/R framework and thus could serve as an easily referenced foundation for the evolution of all downstream documents that rely on this information during investigational product development.<sup>5</sup> The Investigator's Brochure provides a formal source of information from the early introduction of an investigational product into humans. It must convey available information on the investigational product adequately to allow investigators to make an unbiased benefit-risk assessment of the investigational use of the product in the context of the healthy volunteers/patients sitting in front of them.

Several biopharmaceutical companies have already begun proactively completing the sB/R framework and submitting it to FDA as part of the NDA/BLA submission. While FDA has expressed support for this practice, it is currently unclear whether FDA will commit to reviewing a sponsor-proposed sB/R framework or discussing it with the sponsor during review.

Additionally, it is unclear how widespread this is being practiced across the industry.

FDA has expressed an openness to using the sB/R framework during key points of a product's lifecycle prior to approval to ensure transparency on the key areas of judgement for regulatory decision-making, such as the end-of-phase 2 (EOP2) meeting, late cycle meeting, advisory

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<sup>4</sup> BIO, Comments to FDA on Structured Approach to Benefit-Risk Assessment in Drug Regulatory Decision Making, May 7, 2013 <http://www.bio.org/sites/default/files/2013-05-07%20Comments%20on%20Benefit-Risk%205-Year%20Plan%20-%20FINAL.pdf>

<sup>5</sup> Section 7.3.6(b) (Safety and Efficacy) of the E6 guidance describes the need to provide a summary of available information describing the possible risks and adverse drug reactions to be anticipated on the basis of prior experiences with the product under investigation (and with related products). Section 7.3.7 Summary of Data and Guidance for the Investigator, indicates that an overall discussion of the available physical, chemical, pharmaceutical, pharmacological, toxicological, and clinical information on the investigational product(s) is required. This is provided with the overall aim of clarifying the possible risks and adverse reactions, and of the specific tests, observations, and precautions that may be needed in the proper conduct of a clinical trial for a specific product.

<sup>6</sup> E6 Good Clinical Practice: Consolidated Guidance. 1996 <http://www.fda.gov/downloads/drugs/guidances/ucm073122.pdf>

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committee meeting, and/or the pre-NDA/BLA meeting.

FDA currently provides little formal guidance on the content and format of benefit-risk information included in regulatory submissions, and no guidance about structured discussions of benefit-risk using the framework during product development and post-approval. In some instances, FDA has provided no feedback to sponsors about submissions that include the use of quantitative benefit-risk modeling methods, including formal studies of patient preferences.

The lack of information described above provides opportunities to define a clear pathway to increased collaboration between sponsors and FDA to enable consistent, efficient, and transparent benefit-risk assessment.

## **B. Incorporation of Patient Feedback<sup>7</sup>**

FDA has stated that the patient feedback received in the PDUFA V Patient Focused Drug Development meetings is helpful to their understanding of the patient journey.

Individual patient stories help illuminate the day-to-day difficulties of living with a disease, and offer insights into patient perspectives on the benefits and tradeoffs of a potential treatment. However, to ensure patient perspectives become routinely accepted as part of these domains, FDA and sponsors need mechanisms to obtain input efficiently from a large, targeted, and representative cohort of patients in order to justify using that data in regulatory decision making.

Industry has been evaluating methodologies to solicit patient views on medical need and benefit-risk preferences, as well as how to integrate this feedback into the drug development and review stages. The mechanisms used include, but are not limited to, patient and caregiver preference assessments, patient reported outcomes (PRO) tools, and discussions with patient advocacy groups. However, it is unclear how this patient feedback would be used to inform individual product-related regulatory decisions at the reviewer level, and thus patients and industry have asked FDA to provide greater clarity on this issue.

Further, FDA's draft plan states that the assessment involves both quantitative analyses and a subjective qualitative weighing of the evidence, but as written the plan may be misinterpreted to say that all quantitative approaches to benefit-risk assessment are inappropriate. Stakeholders are left with a lack of clarity on the appropriate use of quantitative methods or even how FDA defines "quantitative methods."

Given that the benefit-risk assessment is complex and includes many factors, including patient input, sponsors and patients would benefit from clear guidelines on how the Agency will synthesize patient input, how the review division should use this information at the reviewer level, and how this would be systematically implemented across the Agency.

The sB/R framework holds the potential to serve as a bridge between Patient Focused Drug Development and individual product approvals so that regulatory decisions would be informed by and grounded by patient preference data and other data-driven perspectives on benefit-risk. Because the sB/R framework is being integrated into the standard review template, FDA medical reviewers will be expected to address all of its domains as a matter of course. The framework could be a helpful format for providing the patient's point of view to the medical review team and as a discussion tool with sponsors, patient advocacy groups, and FDA advisory committees.

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<sup>7</sup> In this instance, "patient" includes individual patients, their caregivers, and patient advocacy organizations

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# USE OF THE STRUCTURED BENEFIT-RISK ASSESSMENT FRAMEWORK DURING DRUG DEVELOPMENT, REVIEW, AND POST-APPROVAL

Sponsors that wish to voluntarily draft and submit the sB/R assessment framework to FDA at key stages across the lifecycle of a drug should bear in mind the following considerations:

## A. Early Stage Development (Pre-IND to Phase 1)

Even in the early stages of development, a sponsor has the ability to describe the development rationale for a new medicine in the context of the benefit-risk framework. For example, the substance of this framework may already be established through current criteria used to screen compounds in preclinical and early clinical stages of development when a sponsor is focusing on specific targets. These existing criteria are based on aspects similar to the framework and include an analysis of the condition (disease or symptom), current and expected therapeutic options, medical need, and defined tolerances of acceptable benefits and risks.

This screening exercise, whether based on current criteria or on the sB/R framework, enables sponsors to select compounds based on the characteristics most likely to support a positive benefit-risk assessment in response to the screening criteria for development. Many times this information also is referenced by the sponsor to FDA in the Target Product Profile for a compound or class of compounds. Sponsors also may include this information in the clinical outcome dossiers, such as with PROs. Generally in early development, the framework for selection of compounds may be broad and based on multiple assumptions. It will be important for the sponsor to assess continually the current assumptions and refine the framework as evidence is gained and in consideration of changes in both the internal and external environments.

As the product moves to mid-stage development (phase 2 – EOP2), sponsors should build a firm definition of the medical condition and unmet needs with input from clinicians, FDA, and patients (inclusive of advocacy groups and caregivers). Without a clear definition of the disease/condition and treatment options and organizations gaps, it will be challenging to define the other components of the framework.

To obtain this input, sponsors should consider organizing meetings with a representative group of patients and caregivers, including patient advocacy organizations, to engage in a dialogue around the burden of the condition and the current armamentarium of treatment options. This information should be summarized in the first two lines of the framework, “Analysis of Condition” and “Current Treatment Options.”

In addition to the qualitative feedback collected, sponsors should tap into established scientific expertise to employ methods to gather robust and representative data that could be used in regulatory decision-making, such as patient surveys and stated choice studies, to assess patient preferences and perspectives on benefit-risk considerations and integrate this information into the framework summary.<sup>8</sup>

At this stage in development, the analysis of treatment options should not only encompass currently available treatments, but also include the impact of a potential new therapy. Incorporating

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<sup>8</sup> Methodologies for patient preference assessment and stated choice research may include the following:

- Qualitative research
- Conjoint analysis
- Discrete-choice experiments (DCE)
- Best-worst scaling (BWS)
- Analytic hierarchy process (AHP)
- Ranking techniques
- Structured weighting
- Health-state utility
- Threshold techniques

More information on these survey methods and a catalogue of techniques can be found at <http://mdic.org/pcbcr/>

these perspectives in submissions to FDA, such as the IND briefing materials for milestone meetings (such as EOP1 or EOP2 meetings), will assist the sponsor and FDA in developing an aligned sense of the status quo from the perspective of clinicians, caregivers, and patients. It may also provide an opportunity to identify and discuss potential differences in opinion between the sponsor and FDA early in development that will drive modifications to the development program to ensure appropriate outcome measures are included in the clinical trials so FDA and sponsors could conduct a robust sB/R assessment prior to approval.

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition		
Current Treatment Options		

## B. Mid-to-Late Stage Clinical Development (Phase 2 to Pre-NDA/BLA)

In the middle stage of drug development, the targeted benefit-risk profile of a drug candidate continues to be investigated and refined. While in early development, the focus of the development rationale is focused on defining the target disease state and unmet need, at the mid-stage the focus shifts to designing registration trials that ideally reflect an alignment between the sponsor’s and Agency’s perspectives on the clinical context. The sB/R framework should be a helpful tool to facilitate dialogue between the sponsor and FDA on the evolving understanding of the targeted drug’s benefit-risk profile.

It will be critical that sponsors gain a better understanding of FDA’s thinking about the benefit-risk attributes of a product in order to design trials that address the primary concerns, further elucidate the product’s benefits and risks, and allow the sponsor to predict accurately which compounds are worthy of advancing into phase 3.

During an EOP2 meeting, the sponsor and FDA determine that phase 2 results support proceeding to phase 3, evaluate the design of the phase 3 trials, and identify any additional information necessary to support a marketing application for the use under investigation. Sponsors expect FDA to evaluate and provide a substantive discussion of perceived evidence gaps or data limitations to support a positive benefit-risk ratio for regulatory decision-making. This includes feedback on identification of dose or doses that optimize the safety and efficacy profile.

It is very important that the benefit-risk profile be determined on a case-by-case basis taking into account the merits, harms, and uncertainties of the individual drug within the clinical context of use and unmet medical need.

Sponsors should seek FDA feedback on the phase 3 clinical designs in a way that demonstrates how benefit-risk information will be generated (e.g., clinical trial sources/endpoints, public patient workshops, etc.) in light of data gathered to date and those needed to support a positive ratio.

In order to address the objectives of the EOP2 meeting, sponsors should consider the following prior to an EOP2 meeting:

- As safety and efficacy data are gathered over the course of the development program, sponsors may obtain further patient preference input from patient organizations in the context of the emerging data and gain insight into evolving views of the drug candidate. Companies could consider and implement appropriate measures, such as non-disclosure agreements, to protect any confidential commercial information. This quantitative and qualitative patient feedback should be summarized on the bottom three rows of the framework regarding “Benefit,” “Risk,” and “Risk Management,” as well as the summary assessment. Evidence from clinical trials and



other supporting evidence should be addressed under the “Evidence and Uncertainties” column.

- As the sponsor prepares for the EOP2 meeting, an updated view of the sB/R framework should be included in the EOP2 meeting document. The framework should include elements of data collected to date as well as data uncertainties that will be addressed in Phase 3. This meeting will represent an early opportunity for FDA to hear the voice of the patient as it relates to a specific drug candidate benefit and risk attributes, as well as phase 3 clinical trial development considerations. Examples of phase 3 trial considerations include:
  1. Novel Clinical Study Designs – What is the patient perspective on the size and complexity of proposed phase 3 studies? How can patient feedback enhance recruitment and enrollment strategies in order to accelerate time to study initiation?
  2. Clinical/Surrogate Endpoints and Clinical Outcome Assessments – What value do patients perceive from the use of endpoints that may help accelerate access to the therapy being studied? What is the patient perspective on the clinical outcome measure (clinician rated or PROs)?

<b>Benefit</b>		
<b>Risk</b>		
<b>Risk Management</b>		
<b>Benefit-Risk Summary Assessment</b>		

To most effectively facilitate alignment between the sponsor and the Agency, we would expect that FDA engage with the sponsor to discuss and respond to specific issues regarding the benefit-risk information, and articulate areas where further discussion and alignment is needed.

### C. NDA/BLA Submission

For the pre-NDA/BLA meeting, sponsors should include a preliminary benefit-risk framework in the meeting package. This can serve as a concise synthesis of available data and other attributes/factors that led the sponsor to conclude that the benefit-risk profile is positive and supports the filing of a marketing application.

The framework could be included in all initial NDAs/original BLAs and also in efficacy supplements that support new indications. The framework will provide an opportunity to explain the “why” behind the sponsor’s benefit-risk evaluation, and is critical for driving the content of labeling. It will be incumbent upon the sponsor to collate and present information that bears upon the benefit-risk assessment from sources such as clinical study reports, integrated summaries (Common Technical Document [CTD] Module 2 and ISS/ISE Module 5), the clinical overview (CTD Module 2, Section 2.5.6), and the risk management plan.

Work begun in 2015 to revise ICH M4E, “Enhancing the Format and Structure of Benefit-Risk Information in the Common Technical Document (M4E),”<sup>9</sup> is expected to include greater specificity on the format and structure of benefit-risk information with the goal of harmonizing the presentation of this information in regulatory submissions. It is expected that revisions to M4E will standardize the information inputs that make up the benefit-risk assessment.

<sup>9</sup> International Conference on Harmonisation. Final Concept Paper, “M4E(R2): Enhancing the Format and Structure of Benefit-Risk Information in ICH M4E(R1) Guideline.” [http://www.ich.org/fileadmin/Public\\_Web\\_Site/ICH\\_Products/CTD/M4E\\_R2\\_Efficacy/M4E\\_R2\\_Final\\_Concept\\_Paper\\_27\\_March\\_2015.pdf](http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/CTD/M4E_R2_Efficacy/M4E_R2_Final_Concept_Paper_27_March_2015.pdf)

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition		
Current Treatment Options		
Benefit		
Risk		
Risk Management		
<b>Benefit-Risk Summary Assessment</b>		

## D. Late Cycle Meeting

For products in the NME Review Program, FDA is required hold a Late Cycle meeting. This may occur prior to the Advisory Committee meeting. The intent of the meeting is to enhance communication so that any potential review issues can be raised proactively and, if possible, addressed in the first review cycle by the sponsor.

The briefing package is typically provided by FDA and may be composed of discipline review letters and other related review memos. At this point, sponsors should consider requesting that the FDA provide initial comments on the complete version of the sponsor’s sB/R framework submitted to FDA. The sponsor also should be prepared to discuss what patient preference data has been used to inform the review. For those products not in the NME Review Program, FDA should consider communication during the review process of any considerations of the sB/R framework.

## E. Advisory Committee Meeting

The benefit-risk profile for regulatory decision-making is often both a discussion topic and a question posed at an FDA Advisory Committee meeting. Since it is important to gain alignment between the FDA and the sponsor on key issues to be discussed at an Advisory Committee meeting, early discussion of the framework with the FDA, if possible, can be very beneficial. During early preparation for the Advisory Committee meeting, the sponsor and FDA could each discuss their current thinking around the benefit-risk framework and exchange draft versions of their framework documents. This also would be an opportunity for the sponsor to share with and gain a perspective from the FDA on any novel qualitative or quantitative benefit-risk presentations the sponsor may wish to present at the Advisory Committee meeting.

Both the FDA and the sponsor should provide their views on the benefit-risk profile in the Advisory Committee briefing documents, as these would serve to inform the Committee on the nature of the condition, available treatment options, and benefit-risk considerations from multiple perspectives. In particular, this framework would serve to focus Committee members and the Committee meeting on the complete profile of the medicine and facilitates critical discussions of key efficacy and safety, dosing, labeling recommendations, and post-marketing requirements or commitments. As Advisory Committee meetings are public, to ensure that information is not disclosed prematurely, the sponsor could use a version of the sB/R framework with confidential commercial information redacted.

In addition, the FDA and the sponsor also should consider including the preliminary sB/R assessment framework in their presentations to the Committee.

## F. FDA Approval

The completion of the benefit-risk framework will serve to capture the review team’s careful deliberations and represent expert views transparently while aligning with a review team’s existing processes. The framework is expected to assist the review team to communicate its recommendations to the signatory authority during the review cycle. The framework could also be

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integrated (with or without modifications) by the signatory authority in the decision memo.

Given the FDA-identified desire to communicate more effectively the reasoning behind the Agency's decisions, such as which benefits, risks, or other factors were considered; how the evidence was interpreted; and how the benefits and risks were weighed, the framework should be provided to the sponsor as part of the approval package and also should be made available to the public shortly thereafter by posting on FDA.gov. The framework could be included in review documents or decision memoranda, but in either case, should be readily accessible by the public.

In the event of a Complete Response letter, the framework should be provided to the sponsor as documentation of the same above factors. However, the framework should not be released to the public, consistent with the Agency's treatment of preapproval information as a trade secret and confidential commercial information under existing NIH and FDA regulations, and applicable trade secrets law. Currently, consistent with those regulations and laws, the government protects information about drugs in active development from premature disclosure until they are approved.

## **G. Post-Approval**

The framework could also serve as a tool to prompt discussion of planned risk management activities in the post approval setting. It is recommended that the sponsor maintain an updated version of the benefit-risk framework, incorporating up-to-date safety and efficacy information, as generated for the product during marketing. The framework should be reviewed at least annually so it may serve as the basis for the overall conclusions for annual reports such as the Periodic Benefit-Risk Evaluation Report and Periodic Safety Update Report. Additionally, sponsors implement risk evaluation and mitigation strategies (REMS) during post-approval. If a REMS program exists for a product, the benefit-risk assessment should take the effectiveness of the REMS program into consideration.

In a situation where the sponsor is pursuing additional indications for the product or new dosage forms for the product, the sB/R framework should be developed to support the filing of the supplemental application. The sponsor should discuss with the Agency whether the population or indication is sufficiently different from the original such that a unique benefit-risk profile is appropriate to support the supplemental filing.

## **ADDITIONAL CONSIDERATIONS FOR COMPLETING PROPOSED SB/R FRAMEWORKS**

As industry engages in a lifecycle approach to sB/R assessment, we must be mindful that the sB/R framework is being drafted and developed in a manner that does not formalize any negative or inappropriate regulatory approaches, but rather becomes a structured vehicle for promoting best practices. For instance:

### **A. Embrace the Variation in Patient Perceptions and Preferences**

The benefit-risk process should take into account the heterogeneity of patient views and embrace individual variability and range of patient preferences. A one-size-fits-all approach based solely upon population averages or means may ignore patients willing to tolerate greater risk for greater benefit. It will be important that benefit-risk rules recognize and are sensitive to this patient heterogeneity, and that population mean assessment do not restrict individual judgments and choices.

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## **B. Appropriate Regulatory Comparisons to Current Treatment Options**

While “current treatment options” may be part of FDA’s overall considerations, FDA does not—and should not—approve drugs based on a comparative effectiveness standard. Currently, if a new drug is tested against a placebo and shown to be better—for therapies other than those addressing mortality or serious morbidity—it may be approved. The FDA review paradigm also encourages comparison to available therapies, including those recently launched, but should not drift toward making decisions based on comparative effectiveness.

Ultimately, products must compare favorably to all alternatives to achieve market penetration and success, but sponsors should be cautious about the potential de facto drift of regulatory standards that could result from inappropriate comparative effectiveness analysis related to the benefit-risk framework.

Comparisons of therapies to alternatives also may encourage questionable comparisons that are not based on head-to-head trials. Sponsors are not allowed to make such comparisons in labeling, and the benefit-risk assessments should not encourage reviewers to make such comparisons.

## **C. Encouraging a Balanced Consideration of Benefits vs. Risks**

When the sB/R framework is used across the product lifecycle, it will be important to recognize that in earlier stages of development, the benefit-risk equation is skewed toward safety data, and that a clear and balanced picture of the true benefit-risk profile may become fully clear until phase 3. As clinical data mature and more efficacy data become available in the later stages of clinical development, the benefit-risk calculus shifts from balancing safety against potential benefit to safety versus actual benefit.

Furthermore, typically in labeling, benefits that have only been rigorously proven (sometimes when a primary endpoint is used in more than one trial) can be claimed. In contrast, risks are mentioned often on as little as anecdotal or mechanistic evidence. There are various reasons for this: if this approach is carried into the sB/R framework, it would systematically bias the benefit-risk equation by excluding benefits (that may not have been proven to labeling standards) from consideration while potentially overestimating the risks. Of particular concern, given Agency standards for the inclusion of PROs in labeling, such benefits may not be considered in the balance. As sB/R framework implementation progresses, sponsors should be cognizant of this potential bias and try to ensure appropriate guidelines for considerations of benefits and risks that will minimize bias.

## **CONCLUSION**

Systematic and early use of FDA’s structured benefit-risk framework can be a powerful tool to achieve common alignment among sponsors, patients, and FDA on the benefit-risk considerations underlying an FDA approval decision. Rather than being used just to communicate FDA’s decision in later review stages, the framework should be viewed as an iterative, evolving document that can serve as a decision-support tool to help guide benefit-risk discussions across a product’s lifecycle.

Sponsors and patients would benefit from a defined clear pathway to increased collaboration between sponsors and FDA to enable consistent, efficient, and transparent benefit-risk assessment, as well as guidelines on the methodologies for collecting and analyzing patient preferences and incorporating the patient perspective into the sB/R framework. As industry and FDA more commonly engage in early, proactive discussions of the benefit-risk framework at key stages in drug development, we can achieve a common understanding and vocabulary of how to align on complex benefit-risk considerations in a patient-centric manner.

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## APPENDIX

### Sample Sickle Cell Disease Benefit-Risk Assessment Framework:

The Voice of the Patient: Sickle Cell Report (PDF - 365KB), p. 30  
Public meeting: February 7, 2014; Report date: October 2014

Additional examples are available in the appendix of each Voice of the Patient Report at <http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm368342.htm>

<b>Decision Factor</b>	<b>Evidence and Uncertainties</b>	<b>Conclusions and Reasons</b>
<b>Analysis of Condition</b>	<ul style="list-style-type: none"><li>• Sickle cell disease is a group of hereditary disorders characterized by the distorted crescent or “sickle” shape of red blood cells.</li><li>• The disorder is estimated to affect 100,000 Americans, and occurs in about 1 in 12 African-Americans.</li><li>• Symptoms and can affect every body system. Complications include pain crises, acute chest syndrome, fatigue, difficulty concentrating, and stroke. Over time, blood vessel damage and reduced blood and oxygen flow can result in organ, tissue and bone damage, pulmonary hypertension, vision and hearing loss, and many other effects.</li><li>• The persistence and severity of symptoms and frequent hospitalizations can have extensive negative effects on a patient’s quality of life and ability to function in society. Patients report high levels of social isolation, stigmatization, and difficulty accessing appropriate healthcare.</li><li>• <i>See the Voice of the Patient report for a more detailed narrative</i></li></ul>	Sickle cell disease is a rare, serious disorder that disproportionately affects African-Americans. The disease causes debilitating pain and physical impairment, and takes a significant emotional and social toll on patients’ quality of life.

<p><b>Current Treatment Options</b></p>	<ul style="list-style-type: none"> <li>• Therapies to prevent complications of sickle cell disease include: <ul style="list-style-type: none"> <li>• Hydroxyurea, an FDA-approved treatment to increase production of fetal hemoglobin and reduce the occurrence of sickling-related complications. It is effective for many but not all patients, and side effects include nausea, loss of appetite, hair loss, and kidney or liver complications.</li> <li>• Chronic blood transfusions and exchanges, which are effective in raising normal red blood cell levels and reducing sickle cell complications. Treatment occurs in a hospital setting and requires intravenous access. Side effects include iron overload, alloimmunization, and injection site reactions.</li> <li>• Bone marrow or stem cell marrow transplantation, which can be curative but are associated with significant risks that often limit its use only for patients with significant complications. This treatment is also limited by the availability of appropriate donors.</li> </ul> </li> <li>• Many therapies are used to manage disease complications. <ul style="list-style-type: none"> <li>• Pain crises are often treated in a hospital setting. Prescription and over-the-counter pain relievers are also used for acute and chronic pain.</li> <li>• Penicillin and immunizations are frequently used, especially in children, to prevent infection.</li> <li>• Some patients rely on a restricted diet, supplements and herbal remedies, as well as non-drug therapies such as heat, massage, and relaxation techniques to manage their disease.</li> </ul> </li> <li>• <i>See the Voice of the Patient report for a more detailed narrative</i></li> </ul>	<p>Current treatments are effective in reducing the number and severity of sickle cell disease complications. However, their efficacy varies from patient to patient, and significant treatment burden and side effects and can limit benefits or preclude use of treatment.</p> <p>The disease remains suboptimally managed in a significant portion of the population. Thus, there is a continued need for effective and tolerable treatment options for patients to improve daily functioning and reduce long-term complications.</p>
<p><b>Benefit</b></p>		
<p><b>Risk</b></p>		
<p><b>Risk</b></p>		
<p style="text-align: center;"><b>Summary</b></p>		

# Current Structured Benefit/Risk Process

FDA May Hold One of 20 Patient Focused Drug Development Meetings

FDA Publishes "Voice of the Patient Report" with Sample Framework

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition		
Current Treatment Options		



FDA reviewers complete and publish SB/R framework upon approval

Structure Factor	Findings and Uncertainties	Conclusions and Reasons
Structure Factor		
Structure Factor		
Structure Factor		
Structure Factor		
Structure Factor		

Search for Summary Assessment

Phase 1

Phase 2

Phase 3

FDA Review

Phase 4



# Opportunities for Structured Benefit/Risk Assessment during Drug Development

