Benefit-Risk Assessment and Patient-Focused Drug Development at FDA

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Regulatory Context

• For a drug to be approved for marketing, FDA must determine that the drug is safe and effective
  – Effectiveness standard
  – Analysis of safety = benefits outweigh the risks

• This assessment is informed by an extensive body of evidence, within a very complex context:
  – Underlying condition and current treatment options
  – Uncertainty about how clinical trial extrapolates to real world setting
  – Available risk management tools
  – Dynamic nature of drug’s “life-cycle” after approval
FDA Approach to Benefit-Risk

- Qualitative approach that is grounded in quantification of various data elements. Decisions made at the population level at time of marketing approval:
  - Benefits – Efficacy endpoints from controlled clinical trials
  - Risks – Harms reported in clinical trials and other sources (e.g., spontaneous adverse event reports)

- Decisions on B-R require judgment on the part of the regulator and are influenced by:
  - Statutory/regulatory standards
  - Societal expectations
  - Values and perspectives
Development of a Benefit-Risk Framework

- FDA’s effort to develop a B-R framework coincided with efforts by drug regulators, industry and academia internationally.

- Most of these efforts share common goals:
  - Increase transparency and improve communication of the regulatory decision.
  - Provide structure for identifying critical factors in those decisions.
  - Support, but not supplant, the regulator’s judgment.

- FDA determined that a structured qualitative approach best fit its drug-regulatory decision-making needs:
  - Reflects the reality that B-R assessment is a qualitative exercise grounded in quantification of various data.
Early Framework Development

- Developed a conceptual framework
  - Reviewed challenging prior decisions to identify the range of considerations
  - Interviewed key review disciplines to understand relevant issues
  - Developed question-based prompts to guide framework completion

- Pilot-tested framework in pre-market reviews
  - Evaluated and further refined the framework and its prompts
  - Explored implementation into the review process

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<th>Conclusions and Reasons</th>
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Benefit-Risk Summary and Assessment
CDER’s Benefit-Risk Framework

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Benefit-Risk Summary and Assessment
## CDER’s Benefit-Risk Framework

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<td>- What are the facts and key data?</td>
<td>- How should the data be interpreted?</td>
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<td>- What are the limitations to the evidence?</td>
<td>- What are the implications for the regulatory decision?</td>
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**Benefit-Risk Summary and Assessment**
# B-R Summary and Assessment

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**Benefit-Risk Summary and Assessment**

A succinct, balanced analysis that clearly explains the regulatory recommendation or action:

- Summarizes conclusions from each decision factor, noting the clinical judgment used in interpreting the evidence
- Includes important differences of opinion among the review team how they were resolved
Benefit-Risk in PDUFA V*: FDA’s Commitments

- Publish a 5-year plan that describes FDA’s approach to implement B-R Framework
- Revise review/decision templates and manuals to incorporate FDA’s approach
- Conduct two public workshops on B-R from the regulator’s perspective
- Develop an evaluation plan to ascertain the impact of the B-R Framework
- Conduct 20 public meetings to get patient input on specific disease areas (Patient-Focused Drug Development)

*Fifth authorization of the Prescription Drug User Fee Act
Further Development of the B-R Framework

• Characterizing and Communicating Uncertainty
  – FDA must draw conclusions based on imperfect information (e.g., how well clinical trial data extrapolates to post-market setting or evaluating data from various sources regarding a potential safety signal)
  – Being explicit about the impact of uncertainty is an important part of communicating regulatory decisions
  – Where uncertainty is high, clinical judgment, values, and input from others (patients, advisory committees) may have greater role

• B-R Considerations in the Post-Market Setting
  – Specifying the important B-R considerations when we learn new information about the safety of a product after approval
Patient-Focused Drug Development (PFDD)

- Establishing the therapeutic context is an important aspect of B-R assessment
  - Patients are uniquely positioned to inform understanding of this context
  - Current mechanisms for obtaining patient input are often limited to discussions related to specific applications under review

- PFDD offers a more systematic way of gathering patients’ perspective on their condition and treatment options
  - FDA will convene at least 20 meetings on specific disease areas through September 2017
  - Meetings can help advance a systematic approach to gathering input
Identifying Disease Areas for PFDD Meetings

- FDA sought diversity along the range of diseases encountered in our regulatory decision-making

- Focused consideration on disease areas that:
  - Are chronic, symptomatic, affect functioning/daily activities
  - Currently have few or no therapies, or the available therapies do not directly affect how a patient's feels or functions.
  - Have important aspects not formally captured in clinical trials
  - Reflect a range of severity
  - Have severe impact on identifiable sub-populations (e.g., children)
  - Represent a range in terms of size of the affected population
PFDD meetings for FY2013-2015

**FY 2013 (Conducted)**
- Chronic fatigue syndrome/myalgic encephalomyelitis
- HIV
- Lung cancer
- Narcolepsy

**FY 2014 (Conducted)**
- Sickle cell disease
- Fibromyalgia
- Pulmonary arterial hypertension
- Inborn errors of metabolism
- Hemophilia A, B, and other heritable bleeding disorders
- Idiopathic pulmonary fibrosis

**FY 2015 (Conducted)**
- Female sexual dysfunction

**FY 2015 (to be announced)**
- Alpha-1 antitrypsin deficiency
- Breast cancer
- Chronic Chagas disease
- Functional gastrointestinal disorders
- Parkinson’s disease and Huntington’s disease
Tailoring Each Meeting

• Meetings follow similar, but tailored, design
  – Takes into account current state of drug development, specific interests of FDA review division, needs of the patient population

• Discussion elicits patients' perspectives on their disease and on treatment approaches

• Input is generated in multiple ways:
  – Patient panel comments and facilitated discussion with patients in the audience
  – Interactive webcast and phone line for remote participants
  – Polling questions to aid meeting discussion
  – A federal docket allowing for more detailed comments
A sample of what we ask

• Which symptoms have the most significant impact on your daily life?... On your ability to do specific activities?

• How well does your current treatment regimen treat the most significant symptoms of your disease?

• What specific things would you look for in an ideal treatment for your condition?

• What factors do you take into account when making decisions about using treatments? .... Deciding whether to participate in a clinical trial?
A sample of what we hear

Panelist A: [My attack] starts in the morning, I will wake up like I have been hit by a bus... the pain is so bad, if somebody walks across the floor, I can feel that.

Panelist B: [My biggest problem is] touch. Having my two-year-old granddaughter hug me hurts so much, I would like to push her away, but I don't want to.

Facilitator: We heard various ways that pain manifests. 
Asks for show of hands for a few types. Any pain not yet described that you want to talk about?

Participant A: A burning pain... like the burning you get from exercise, I get that from just standing up or walking in the kitchen...

Participant B: Headaches... if you can imagine making a mold of your head that’s a quarter inch too small all around and put it on. It’s crushing from every direction.
Patient stakeholders have taken initiative

- Spread word through websites, social media or flyers
- Facilitated registration or docket submission
- Organized transportation, pre or post-meeting get-togethers
- Conducted webinars to prepare participants to “use their voice most effectively”
- Conducted surveys
Patient-Focused Drug Development
Meeting Outcomes

• Each meeting results in a report* that faithfully captures the input from the various information streams
• FDA staff will consider this input when conducting B-R assessments for products under review
• Input could support other aspects of drug development (e.g., help identify of areas of unmet need, develop clinical outcome tools that better address patient needs)

*See [http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm368342.htm](http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm368342.htm)
Reflecting on our experience to date

• Patient input has been powerful and insightful

• Meetings can be effectively tailored to fit the needs and interests of FDA and the patient community

• We continually learn how to create maximum value in this public meeting process:
  – Reach a broad population reflecting range of experiences, perspectives
  – Enable patients to feel that their perspectives have been shared
  – How to represent the input in an accessible summary report

• There is external interest in seeing expanded efforts to gather and use patient input in drug development and review
Planning for Future PFDD Meetings in FY 2016-2017

FDA published FR notice* requesting public comment (by December 5th) on preliminary list of potential disease areas--as well as comment on diseases not represented on this list-- for the remaining meetings under PDUFA V

- Achondroplasia
- Alopecia areata
- Autism
- Autoimmune disorders treated with immune globulins
- Depression
- Diabetic foot infection
- Hereditary angiodema
- Melanoma, specifically unresectable loco-regional disease
- Neurologic disorders treated with immune globulins
- Nontuberculous mycobacterial infections
- Ovarian cancer
- Patients who have received an organ transplant
- Primary humoral immune deficiencies
- Pruritis
- Sarcopenia
- Thrombotic disorders