Public Meeting on Benefit-Risk Assessments in Drug Regulatory Decision-Making

September 18, 2017
Welcome

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Office of Strategic Programs
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

September 18, 2017
Agenda

• Welcome and Opening Remarks
• Session 1: Regulatory and Industry Experiences with Benefit-Risk Assessment Approaches
• Lunch
• Session 2 – Approaches to Incorporating Patient Perspectives into Benefit-Risk Assessment
• Session 3 – Special Topics in Benefit-Risk Assessment
• Open Public Comment
• Closing Remarks
Opening Remarks

Richard Moscicki, MD
Deputy Center Director for Science Operations
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

September 18, 2017
Session 1
Regulatory and Industry Experiences with Benefit-Risk Assessment Approaches
Overview of FDA’s Benefit-Risk Framework and its Implementation

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Office of Strategic Programs
Center for Drug Evaluation and Research (CDER)
U.S. Food and Drug Administration (FDA)

Public Meeting on Benefit-Risk Assessments in Drug Regulatory Decision-Making

September 18, 2017
Regulatory Context

• For a drug or biologic* to be approved for marketing, FDA must determine that the drug is effective and that its benefits outweigh its risks to the population.

• 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
  – Laws and regulations

*For simplicity, the term “drug” is used in this presentation to mean both drugs and biologics.
Historical Context

• In 2009, FDA began work to develop a structured benefit-risk framework for human drug review

• FDA’s goals were two-fold:
  – External: Better communicate the reasoning behind CDER’s decisions
  – Internal: Ensure the “big picture” is kept in mind throughout a complex, detailed review

• 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 the quantification of various data
  – More rigorously communicates the basis for decisions, in words
  – Flexible to accommodate more complex supporting quantitative analyses that can aid expert judgment
FDA’s Benefit-Risk Framework for human drug review

**Benefit-Risk Integrated Assessment**

<table>
<thead>
<tr>
<th>Benefit-Risk Dimensions</th>
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<tr>
<td><strong>Dimension</strong></td>
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<tr>
<td>Evidence and Uncertainties</td>
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<tr>
<td>Conclusions and Reasons</td>
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- Analysis of Condition
- Current Treatment Options
- Benefit
- Risk
- Risk Management
Sample Framework Questions

Analysis of Condition

– How does severity vary across the specific demographics or sub-populations?
– How, if at all, does the condition affect patients’ functioning or quality of life, across the spectrum of severity?

Current Treatment Options

– Describe the other therapies used to treat the condition, including off-label products and non-pharmacological therapies.
– How well is the patient population’s medical need being met by currently available therapies?

Benefit

– What is the clinical relevance of the clinical endpoints? How do they relate to how a patient feels, functions or survives?
– How clinically meaningful is the benefit shown to: a) the overall population of patients; and b) any specific subset of patients?
Sample Framework Questions

Risk

– Characterize the safety concerns identified in the development program.
  • E.g., Is there a range in the severity of the risk? Is it reversible when treatment is stopped?
– How might the product’s safety profile change in the post-market setting, if the product is approved for this indication?
– What are the major uncertainties regarding the safety concerns identified?

Risk Management

– Which safety concerns can be appropriately addressed through product labeling?
– Are there any serious safety concerns that may require risk management beyond labeling?
– How might multiple risk management elements fit together into a reasonable and appropriate strategy?
Desired Benefits of the BRF

• Provide a clear and concise snapshot of the regulatory decision, and how the demonstrated benefits were weighed against the risks

• Highlight the aspects of the clinically meaningful efficacy and safety data most relevant to decision making

• Faithfully capture the review team’s careful deliberations and represents expert views transparently, including differences of opinion

• Improve transparency in the decision-making process

• Provide an accessible record of the decision for reference in future reviews
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 at least 20 public meetings in fiscal years 2013-2017 to get patient input on specific disease areas (Patient-Focused Drug Development)
# Overview of PDUFA V Implementation

<table>
<thead>
<tr>
<th>Date</th>
<th>Description</th>
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<tr>
<td>Feb 2013</td>
<td>Published Draft Implementation Plan</td>
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<tr>
<td>May 2013</td>
<td>CBER integrated the BRF into review templates for original biologics license applications (BLAs) and BLA efficacy supplements</td>
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| Sept 2013     | CDER established the Benefit-Risk Implementation Committee (BRIC)  
• Began process to revise clinical review and memo templates                                                                                     |
| Feb/May 2014  | 1<sup>st</sup> public meeting: Characterizing and Communicating Uncertainty in Assessment of Benefits and Risks                                                                                        |
| Mar 2015      | CDER implemented new template for reviews of new molecular entities (NME) /original BLAs  
• Launched on-going staff training and individual support                                                                                          |
| Sept 2015     | Initiated an evaluation of the BRF implementation (contracted)                                                                                                                                             |
| Sept 2017     |  
• CDER broadened implementation to a wider set of applications  
• Completed BRF evaluation project  
• 2<sup>nd</sup> public meeting on Experiences with Benefit-Risk Assessment                                                                           |
Frameworks are starting to appear in posted reviews
(drug reviews are found at drugs@FDA)

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<tr>
<th>Analysis of Condition</th>
<th>Current Treatment Options</th>
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<tr>
<td><strong>Schizophrenia</strong> is a severe, chronic, disabling mental illness affecting approximately 1% of the population. Onset of illness is typically in early adulthood. The disease is characterized by abnormal behavior and psychosis. Symptoms are categorized as positive (e.g., hallucinations and delusions) and negative (e.g., social withdrawal, lack of emotion, energy, and motivation) domains. Most medications have predominant effects on positive symptoms. Although there are a number of approved treatments for this condition, an individual patient may require several trials with different antipsychotic drugs before an effective and reasonably-tolerated treatment is identified.</td>
<td><strong>Schizophrenia</strong> is a severe and debilitating illness. For many patients, existing treatment options are unable to adequately control their symptoms, or may cause intolerable adverse reactions.</td>
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| **A number of “typical” and “atypical” antipsychotics are currently available for the treatment of schizophrenia. Some of the relevant class safety issues for antipsychotics include extrapyramidal side effects, tardive dyskinesia, neuroleptic malignant syndrome, hyperprolactinemia, orthostatic hypotension, weight gain, metabolic changes, and blood dyscrasias. The atypical antipsychotics have been associated more with weight gain, hyperglycemia and hyperlipidemia side effects compared to the typical antipsychotics.** | **Although there are a number of approved atypical antipsychotics currently on the market, individual patient response to a given antipsychotic cannot be predicted. For an individual patient, several trials of different drugs are often required before an effective treatment can be identified. Some patients do well for some period of time on one drug, only to develop side effects, requiring a switch to another drug. There are also some patients for whom an effective treatment has yet to be identified, despite multiple trials. Thus, having additional treatment options is valuable.** |

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<th><strong>Benefit</strong></th>
<th><strong>Risk</strong></th>
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| The Sponsor conducted two adequate and well-controlled studies to assess the efficacy of brexpiprazole in the treatment of schizophrenia.  
- In Study 231, both the 2 mg/day (LS mean difference=−8.7, p<0.0001) and 4 mg/day (LS mean difference=−7.6, p=0.0006) dosage groups showed statistically greater improvement on the PANSS.  
- In Study 230, only the 4 mg/day dosage group was statistically superior to placebo (LS mean difference=−6.5, p=0.002). The brexpiprazole 2 mg/day group did not demonstrate superiority to placebo, although it did show a greater numerical improvement.  
- Pooling data across the two pivotal Phase 3 trials supports the concept that the 2 mg/day dosage is effective. | **Safety results were similar in the MDD and schizophrenia development programs, and similar to the known safety profile of atypical antipsychotics as a class; no unique safety concerns were identified.** |

(e.g., REXULTI, table portion only)
Benefit-Risk in PDUFA VI

• Update plan for continued implementation of structured benefit-risk assessment during FY 2018-22

• Draft guidance on benefit-risk assessment for new drugs and biologics
  – Articulate FDA’s decision making context and framework, throughout the human drug lifecycle
  – Discuss appropriate interactions between a sponsor and FDA during drug development to understand the therapeutic context regarding relevant regulatory decisions at various stages of drug development and evaluation
  – Discuss appropriate approaches to communicate to the public FDA’s thinking on a product’s benefit-risk assessment (e.g., during Advisory Committee meetings)

• Evaluate implementation of the Benefit-Risk Framework, using the PDUFA V evaluation as a baseline

• Revise relevant manuals/standard operating policies and procedures (MAPPs/SOPPs) to incorporate the benefit-risk framework approach
Other Opportunities

• Make BRFs more easily accessible on FDA’s website

• Explore use of more technical approaches within the qualitative framework to inform benefit-risk assessment in targeted cases
  – Example: structured techniques to characterize uncertainties inherent to the assessment and evaluate their implications on the regulatory decision
  – In what types of situations are approaches appropriate and valuable?

• More effectively incorporate patient experience data into drug development, evaluation, and benefit-risk assessment
  – Focus of 21st Century Cures Act and PDUFA VI
Acknowledgements

Theresa Mullin
Patrick Frey

CDER’s Decision Support and Analysis Team
Pujita Vaidya, Meghana Chalasani,
Sara Eggers, Graham Thompson, Shanon Woodward

Benefit-Risk Implementation Committee
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Patrick Frey, Hylton Joffe, Sally Loewke, Amy McKee, Theresa Mullin,
Abhilasha Nair, Vaishali Popat, Ramesh Raman, Jeff Roberts,
Bob Temple, Ellis Unger, Susanne Walker

CDER and CBER leadership
Objectives

• Overview of CDER’s Benefit-Risk Framework (BRF) from concept to the present day
• Discuss case study 1 (concept)
  – Liraglutide approved January 2010
• Discuss case study 2 (present day)
  – Nusinersen approved December 2016
CDER’s Benefit-Risk Framework

• In 2009, CDER began work to develop a structured benefit-risk framework for new drug review

• CDER’s goals were two-fold:
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Adapted from Dr. Sara Eggers’ presentation
Liraglutide as Case Study 1

- GLP-1 receptor agonist with extended duration of action indicated for the treatment of type 2 diabetes mellitus (T2DM)
- Approval on January 25, 2010 predated implementation of BR framework but review team took part in interviews to determine approach to BR assessment
Liraglutide as Case Study 1

• Lowered HbA1c (efficacy) but had safety concerns:
  – 2-yr rodent carci studies identified potential risk of medullary thyroid cancer
  – NDA submitted just prior to publication of FDA guidance for evaluation of CV safety of all T2DM therapies
  – Public AC meeting April 2, 2009: split vote for approval
  – Differing B-R conclusions within FDA

• BR assessment for lira glutide existed throughout several memos:
  – 17-pg Office, 45-pg Division, 63-pg CDTL, 500+ pgs Medical Officer, 700+ pgs Pharm/Tox
  – 4-page NEJM perspective published March 2010
Analysis of Framework in 2016

CDER New Molecular Entity (NME) and New Biologic License Application (BLA) Filings and Approvals

<table>
<thead>
<tr>
<th>Calendar Year</th>
<th>PDUFA IV</th>
<th>PDUFA V</th>
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<tbody>
<tr>
<td>2007</td>
<td>18</td>
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<td>2008</td>
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<tr>
<td>2015</td>
<td>45</td>
<td>35</td>
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<tr>
<td>2016*</td>
<td>22</td>
<td>41*</td>
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22 NMEs/BLAs approved in 2016

Expedited development/review applied in 73% of these applications

- 8/22 (36%) were first-in-class
- 9/22 (41%) approvals were for rare disease
- 8/22 (36%) received fast track designation
- 7/22 (32%) received breakthrough designation
- 15/22 (68%) received priority review
- 6/22 (27%) received accelerated approval
Nusinersen as Case Study 2

• Approval in Dec 2016 after 1st B-R public workshop, two revisions to review template for BRF, and evaluation of BRF implementation

• Presentation focuses on Office and Division Directors’ BRFs.
  – Reader encounters BRF first in review package posted at Drugs@FDA
  – BRFs were 4 and 5 pages long, respectively
CDER’s Benefit-Risk Framework

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Adapted from Dr. Sara Eggers’ presentation
Spinal muscular atrophy (SMA) is a rare and serious disease resulting from deletion or mutation of the SMN1 gene which codes for a protein that helps maintain motor neurons.

SMN2 is a related gene that can produce this protein to compensate for SMN1 defect but most copies of SMN2 pre-mRNA lack exon 7 which leads to a truncated protein that is easily degraded.

Clinical heterogeneity in SMA depending on the number of copies of SMN2 gene inherited.

- 1 copy - death shortly after birth; 2 copies - unable to sit unassisted with survival < 2yrs; ........more than 4 copies can have normal life expectancies and mild muscle weakness
Nusinersen as Case Study 2

- No approved therapies for SMA
- Nusinersen is an anti-sense oligonucleotide that binds to the SMN2 pre-mRNA and promotes inclusion of exon 7 allowing for production of functional protein
- Approval based on interim analysis of controlled trial in patients with infantile-onset SMA (2 copies of SMN2)
  - 40% on drug met motor milestone development responder definition vs 0 in sham control arm ($p<0.0001$)
  - Trial stopped early and all patients switched to active treatment
Nusinersen as Case Study 2

• Other supportive data included:
  – Topline results from controlled trial in later-onset SMA (3 copies of SMN2) stopped early based on highly statistically significant effect on a functional motor scale assessment (p=0.000002).
  – Open-label trials in less severe SMA (up to 4 copies of SMN2)

• Safety data limited by small patient population but approval leveraged knowledge of other oligonucleotides in development. Concerns included thrombocytopenia/bleeding, proteinuria, and effects on growth.
Favorable BR Assessment for Nusinersen

• Benefit established from trial that “has many of the important characteristics of an adequate and well-controlled study that can, by itself, provide substantial evidence of effectiveness...”

• Rare disease and unmet medical need called for regulatory flexibility as shown in willingness to accept interim analysis of pivotal trial, top-line data from 2nd trial, and open-label studies which together led to full approval of nusinersen for the treatment of SMA in pediatric and adult patients
CDER’s Benefit-Risk Framework

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Adapted from Dr. Sara Egger’s presentation
Nusinersen as Case Study 2

In considering the benefit, it is important to convey realistic expectations with respect to the effect size. Although a 41% response rate (compared to 0%) sounds impressive on face, it means that (41%) of nusinersen-treated patients meeting a responder definition (based on achievement of motor milestones), vs. 0/27 (0%) of controls (p<0.0001). Secondary endpoints, although presented only descriptively according to the statistical analysis plan, consistently support a treatment benefit.

But it should be kept in mind that the vast majority of patients did not achieve this milestone, and no patient became able to stand unassisted or walk (one patient stand with assistance). Thus, although the drug represents an unprecedented advance for individuals with SMA, it does not represent a cure. For example, among nusinersen-treated patients (6% of patients gained the ability to sit without assistance, a feat that almost never occurs in individuals with only 2 copies of the SMN2 gene), the majority of patients had a modest response or no response at all.
Conclusions

• CDER’s structured Benefit-Risk Framework has led to:
  – More transparency in regulatory decision-making process
  – Balanced communication to public of what to expect from the approved therapy

• CDER’s BRF applied to all applications but only approved ones are shared publicly
Benefit-Risk Framework

Independent Assessment

September 18, 2017

Contract HHSF233201510027I, Order HHSF22301001T
Introduction
**Purpose**

- Fulfill FDA commitment under PDUFA V
- Examine usefulness of Benefit-Risk Framework (BRF) in facilitating:
  - Consistent, balanced consideration of benefits and risks
  - Training, communications, and decision-making within FDA
  - Communication of benefits and risks to external audiences
Examined BRFs written for defined cohort of novel drug applications\(^1\) \((n=43)\)

Reviewed content, format, clarity, and understandability

Conducted interviews with:

- FDA staff\(^2\) \((n=104)\)
- Applicants\(^3\) \((n=45)\)
- Patients, health organizations, healthcare providers \((n=154)\)

\(^1\) New Molecular Entity (NME) NDAs and original BLAs received 3/1/2015 to 2/29/2016 with FDA decision by 5/17/2017.

\(^2\) Medical officers, primary clinical reviewers, Cross-Discipline Team Leaders, Division Directors, and Office Directors.

\(^3\) Representatives of drug developers whose products received FDA approval.
Results Highlights
Usefulness to FDA

- 75% of FDA interviewees stated that BRF is useful in one or more ways
  - Organizing thinking about benefits and risks
  - Reminding reviewers to cover key points
  - Training newer reviewers
  - Communicating benefit-risk analysis in a concise, standardized fashion

- 25% thought that primary use is to communicate benefit-risk analysis externally
Results Highlights

Usefulness to Applicants

• Applicants interviewed felt that BRF is useful in one or more ways

  ✓ Verify alignment between their and FDA’s experiences with product review

  ✓ Communicate concise summary of product review to management and partners

  ✓ Glean insights to improve future development efforts, application materials, and postmarketing activities

• Would also like to receive BRFs for non-approved applications (privately, not publicly)
Results Highlights

Usefulness to External Stakeholders

• External stakeholders interviewed stated that BRF is useful in one or more ways
  ✓ Provide transparency in FDA’s reasoning and decision-making
  ✓ Understand therapy and decide whether to use/prescribe
  ✓ Interpret and share information about new therapies
  ✓ Shape policy, advocacy, and research efforts
  ✓ Understand opinion of credible, objective experts at FDA

• Would also like BRFs for efficacy supplements
• Would like BRFs to be easier to find
Results Highlights

Content

• About the BRFs they read, most interviewees felt that:
  ✓ Main topics are the right ones to cover
  ✓ Content accurately reflects information in full review document
  ✓ Consistency in how much detail BRFs contain could be better

• Less common opinions:
  ✓ BRFs have too many details or redundancies
  ✓ BRFs could include more patient perspectives, clinical considerations, review issues, or quantitative assessment
Results Highlights

Format

• Most interviewees felt that:
  ✓ BRF format is effective in organizing and presenting content
  ✓ BRF format helps make content usable
  ✓ FDA could enhance format to be even more user-friendly (suggestions later in presentation)

• Less common opinions:
  ✓ BRF format could be streamlined
  ✓ BRF format could be expanded
Results Highlights

Clarity and Understandability

• Most interviewees felt that:

  ✓ Content is clear and understandable
    (with effort for some non-technical audiences)

  ✓ Format contributes to clarity and understandability

  ✓ FDA could enhance format to further improve clarity and understandability (suggestions later in presentation)
Findings and Recommendations
Findings and Recommendations

**BRF Successes**

- Effective in communicating reasoning behind FDA’s regulatory decision
- Useful and worthwhile for FDA, applicants, patients, health organizations, and healthcare providers
- Clear and understandable to most audiences – despite major differences in education and roles
Findings and Recommendations

Potential BRF Refinements

- Develop BRFs for more types of applications
- Post BRFs as easy-to-find standalone documents
- Improve consistency in level of detail in BRFs
- Refine template to enhance presentation of content:
  - Add concise, well-structured conclusion statement
  - Add link to acronyms / glossary
  - Add bold lead-in headings to paragraphs in summary
  - Standardize on bullets in left column, short conclusion statements in right column
REGULATORY PERSPECTIVE ON THE NEW ICH GUIDELINE AND THE EVOLVING NATURE OF BENEFIT-RISK ASSESSMENT

Patrick Frey
Chief of Staff, Office of New Drugs
Center for Drug Evaluation and Research, FDA
Background

• Regulatory authorities approve drugs that are demonstrated to be safe and effective for human use
• Definition of “safe” has historically been interpreted as “benefits outweighing risks of the drug”
• Benefit-risk assessment is the fundamental basis of regulatory decision-making
• In the last several years, providing greater structure for benefit-risk assessment has been an important topic in drug regulation
Background, continued...

• M4E(R1) had general guidance regarding the expected content of CTD Section 2.5.6 “Benefits and Risks Conclusions”

• But, there was limited additional guidance to aid industry in structuring their benefit-risk assessment. Therefore, regulators saw variation in submissions.
2.5.6 Benefits and Risks Conclusions

The purpose of this section is to integrate all of the conclusions reached in the previous sections about the biopharmaceuticals, clinical pharmacology, efficacy and safety of the medicinal product and to provide an overall appraisal of the benefits and risks of its use in clinical practice. Also, implications of any deviations from regulatory advice or guidelines and any important limitations of the available data should be discussed here. This assessment should address critical aspects of the proposed Prescribing Information. This section should also consider the risks and benefits of the medicinal product as they compare to available alternative treatments or to no treatment in illnesses where no treatment may be a medically acceptable option, and should clearly indicate the expected place of the medicinal product in the armamentarium of treatments for the proposed indication. If there are risks to individuals other than those who will receive the drug, these risks should be discussed (e.g., risks of emergence of drug-resistant bacterial strains with widespread use of an antibiotic for minor illnesses). The analyses provided in previous sections should not be reiterated here. This section often can be quite abbreviated when no special concern has arisen and the drug is a member of a familiar pharmacological class.

This analysis of benefits and risks is generally expected to be very brief but it should identify the most important conclusions and issues concerning each of the following points:

- the efficacy of the medicinal product for each proposed indication;
- significant safety findings and any measures that may enhance safety;
- dose-response and dose-toxicity relationships, optimal dose ranges and dosage regimens;
- efficacy and safety in sub-populations, e.g., those defined by age, sex, ethnicity, organ function, disease severity, and genetic polymorphisms;
- data in children in different age groups, if applicable, and any plans for a development programme in children;
- any risks to the patient of known and potential interactions, including food-drug and drug-drug interactions, and recommendations for product use;
- any potential effect of the medicinal product that might affect ability to drive or operate heavy machinery.

Examples of issues and concerns that could warrant a more detailed discussion of benefits and risks might include:

- the drug is for treatment of a non-fatal disease but has known or potential serious toxicity, such as a strong signal of carcinogenicity, teratogenicity, pro-arrhythmic potential (effect on QT interval), or suggestion of hepatotoxicity;
- the proposed use is based on a surrogate endpoint and there is a well-documented important toxicity.

Safe and/or effective use of the drug requires potentially difficult selection or management approaches that require special physician expertise or patient training.

2.5.7 Literature References

A list of references used, stated in accordance with the current edition of the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, International Committee of Medical Journal Editors (ICMJE) 1 or the system used in "Chemical Abstracts", should be provided. Copies of all references cited in the Clinical Overview should be provided in Section 5.4 of Module 5.

1 The first edition of the Uniform Requirements for Manuscripts Submitted to Biomedical Journals was issued by the Vancouver Group and was published in 1978.

Acknowledgement to Francesco Pignatti, EMA & M4E EWG member
Expert Working Group (EWG) Membership

- European Commission (EC)
- Pharmaceutical Research and Manufacturers of America (PhRMA)
- U.S. Food and Drug Administration (FDA)
- Ministry of Health, Labour and Welfare (MHLW)
- Japan Pharmaceutical Manufacturers Association (JPMA)

- European Federation Pharmaceutical Industries and Associations (EFPIA)
- SwissMedic
- DOH of Chinese Taipei
- DRA of Korea
- DRA of Brazil
- DRA of Australia
- World Self-Medication Industry (WSMI)
EWG consensus of general principles for a revised guideline

• A revised Section 2.5.6 guideline should be concise and not prescriptive; it should suggest elements for consideration by an applicant in the benefit-risk assessment

• The new guideline should not specify methods for the benefit-risk assessment, nor should it specify the review approach used by a regulator

• Section 2.5.6 should be consistent with other benefit-risk relevant ICH guidelines (e.g., ICH E2C(R2) (PBRER))
EWG consensus on general principles for submitted Section 2.5.6

• Section 2.5.6 should represent the thought process behind the applicant’s weighing of benefits and risks
• It should communicate this thought process to the regulator
• It should not present new efficacy or safety data
Revised Section 2.5.6 Structure

• 2.5.6 Benefits and Risks Conclusions
  – 2.5.6.1 Therapeutic Context
    • 2.5.6.1.1 Disease or Condition
    • 2.5.6.1.2 Current Therapies
  – 2.5.6.2 Benefits
  – 2.5.6.3 Risks
  – 2.5.6.4 Benefit-Risk Assessment
  – 2.5.6.5 Appendix
Notable aspects of M4E revision:
2.5.6.1 Therapeutic Context

• Discussion includes:
  – Disease or Condition—aspects of the disease that are most relevant to the intended population across the spectrum of disease severity
  – Current Therapies—major therapies in the intended population and the medical need for a new therapy
• Limitations or uncertainties in understanding the condition or therapies should be discussed
• Information about disease severity in subpopulations should be considered
Notable aspects of M4E revision: 2.5.6.2 Benefits and 2.5.6.3 Risks

- Use of terms ‘Key Benefits’ and ‘Key Risks’ aligns with ICH E2C(R2) (PBRER)
- Suggestions for the types of benefits and risks to consider when identifying key benefits and key risks
- Suggestions for characteristics of benefits and risks to consider when identifying and describing the key benefits and key risks
- Strengths, limitations, and uncertainties of the benefit and risk information should be considered and discussed
Notable aspects of M4E revision:
2.5.6.4 Benefit-Risk Assessment

• No prescribed approach for the assessment
• A descriptive approach will generally be adequate
• Applicants may use other methodologies to express the benefit-risk assessment quantitatively
• Detailed presentations of the methodology may be submitted in an appendix to 2.5.6, although a summary and explanation of the conclusions should be included in 2.5.6
Notable aspects of M4E revision:

2.5.6.4 Benefit-Risk Assessment, cont.

- Summary tables and graphical displays may be considered to communicate the benefit-risk assessment.

- Information about patient perspectives may be considered, to include:
  - Descriptive information on patient attitudes and preferences with respect to therapeutic context, benefits, and risks.
  - Information obtained directly from patients or indirectly from other stakeholders using qualitative, quantitative, or descriptive methods.
Moving from M4E(R1) to M4E(R2)...

Acknowledgement to Francesco Pignatti, EMA & M4E EWG member
Moving from M4E(R1) to M4E(R2)...

Acknowledgement to Francesco Pignatti, EMA & M4E EWG member
Outlook

• Benefit-risk assessment is a rapidly evolving field with variations in experience and expertise
• New 2.5.6 captures pan-regional thinking on content, format, and the flexibility to apply different approaches to benefit-risk assessment
• The EWG looks forward to observing as the new Section 2.5.6 is implemented in regulatory submissions

www.fda.gov
So...what are regulators seeing with submitted Sections 2.5.6?
Recently submitted Sections 2.5.6

• ~50% of submitted NME NDAs and Original BLAs YTD used the new guideline
• Clinical Overview length: 34-149 pages
• Section 2.5.6 length: 3-21 pages
• On average, Section 2.5.6 length was about 10% of the entire Clinical Overview
EMA framework for benefit-risk assessment

FDA Public Meeting on Benefit-Risk Framework Implementation; 18 September 2017

Francesco Pignatti, European Medicines Agency (EMA)
Contents

• From “quality, safety and efficacy” to benefit-risk assessment
• EMA framework for benefit-risk assessment
• Quantitative methods: Are we ready?
• Patient preferences; uncertainties
• Conclusions, perspective

Disclaimer: The views presented are personal
Benefit-risk assessment example: Marketing Authorisation for Taxotere (docetaxel, 1995)

The Committee for Medicinal Products for Human Use (CHMP) Members have, during the review process, agreed that the application contains sufficient clinical data to support clinical safety and efficacy allowing a positive recommendation for granting marketing authorisation.
Benefit-risk assessment example: Marketing Authorisation for Ninlaro (ixazomib, 2016)

How was efficacy and safety assessed?

Senior assessor:

«First start from the benefits: “Is there a clinically significant benefit?”

If yes, look at adverse events. Are they acceptable for the patient?»

Benefit-risk methodology project Work package 1 report (2009) (WC500109478.pdf);
http://www.ema.europa.eu

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What has changed?

- Publicity about the reasons and rationales that play a part in decisions

- Research methodologies of benefit-risk balance
  - Involve experts in decision theory and behavioural sciences (L. Phillips, B. Fasolo)
  - Improve consistency, transparency and communication of B/R
  - Switch from “implicit” to “explicit” decision making


From Quality, Safety, Efficacy to Benefit Risk Balance

Legal framework: An application ids to be refused if...

65/65/EEC
Harmful or, Therapeutic efficacy is lacking

75/318/EEC
Harmfulness and therapeutic efficacy can only be examined in relation to each other;
Therapeutic advantages must outweigh potential risks

2004/27/EC
The risk-benefit balance is not considered to be favourable
Therapeutic efficacy is insufficiently substantiated
Benefit-Risk: A decision problem

- **Problem**: Is Benefit-Risk balance positive?
- **Objective**: Goal of therapy? Attributes
- **Alternatives**
  - Approve; reject; (reframe, e.g., restrict indication)
- **Consequences of alternatives**
  - Estimated based on data
- **Trade-offs**
  - Based on value judgments
- **Uncertainties (and how to cope with them)**
- **Risk-attitude and Linked decisions**
EMA Benefit-Risk Assessment Template

- **Benefits**
  - Beneficial effects
  - Uncertainty

- **Risks**
  - Unfavourable effects
  - Uncertainty

**Effects Table**
- Importance of effects
- Benefit-risk balance

Structured benefit-risk assessment
Benefit-risk assessment toolkit
Quantitative methods: Are we ready?

Different opinions for and against

Complex regulatory environment, unlikely to change.

May be useful as communication tool:

• Companies encouraged to explore with quantitative methods and submit alongside traditional approaches

Role of quantitative approaches currently unclear for reviewers
Complexity of our process

Different views about quantitative methods

<table>
<thead>
<tr>
<th>Against</th>
<th>In favour</th>
</tr>
</thead>
<tbody>
<tr>
<td>Require more effort</td>
<td>Easy to update</td>
</tr>
<tr>
<td>Does not reflect mental process</td>
<td>Intuition can lead to error and bias</td>
</tr>
<tr>
<td>Highly subjective</td>
<td>Subjectivity is handled explicitly</td>
</tr>
<tr>
<td>“Black box”</td>
<td>Easily understood, transparent</td>
</tr>
<tr>
<td>High precision is unattainable</td>
<td>Uncertainty can be managed explicitly</td>
</tr>
<tr>
<td>Oversimplification (“single number”)</td>
<td>A single number summary is an abuse of the model</td>
</tr>
<tr>
<td><strong>Whose values?</strong> Authority of decision-makers questioned</td>
<td>Impact of different inputs can be explored</td>
</tr>
</tbody>
</table>

Weighing benefits and risks

- Benefit-risk trade-off: the willingness to forego the achievement of one objective against the achievement of another objective

- Requires **value judgments** about the acceptability of trade-offs

- If a group of reasonable and well-informed patients accepts tradeoff, this may support a favourable benefit-risk profile

---

EMAP Framework of interaction with patients

- 2014 revised framework of EMA interaction with patients¹
- Facilitate participation of patients in benefit/risk evaluation
- Little regulatory experience with methods to elicit patient preferences
- Stated preference studies to explore heterogeneity and acceptability of treatments


D. Postmus et al. (in press). Individual trade-offs between possible benefits and risks of cancer treatments: Results from a stated preference study with multiple myeloma patients. The Oncologist.
Decision making under uncertainty

• “Uncertainty”: often used but ill-defined
• What blocks reviewers from taking a decision
• Framework for classifying regulatory uncertainties is missing
• Communicate uncertainties
• Identify coping strategies
Identifying types of uncertainties, and coping strategies

Source

what causes the uncertainty

Issue

what the uncertainty is about

Coping strategy

dealing with the uncertainty


Zafiropoulos N et.al. (2017) Uncertainties and coping strategies in the regulatory review of orphan medicinal products. CEN-ISBS 2017 (abstr.)
Possible framework for uncertainty and copying strategy

<table>
<thead>
<tr>
<th>Source</th>
<th>Issue</th>
<th>Coping strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not enough data</td>
<td>Outcome (benefits; risks)</td>
<td>Reduce</td>
</tr>
<tr>
<td>Unreliable data</td>
<td>Quantitative</td>
<td>Ask new data</td>
</tr>
<tr>
<td>Conflicting data</td>
<td>Subpopulation</td>
<td>Ask new analyses</td>
</tr>
<tr>
<td>Lack understanding of relevance of data</td>
<td>Long term</td>
<td>Ask for explanations</td>
</tr>
<tr>
<td></td>
<td>Real-life</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Relative effect</td>
<td>Use assumptions</td>
</tr>
<tr>
<td></td>
<td>Other</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Outcome (benefit-risk optimisation)</td>
<td>Acknowledge</td>
</tr>
<tr>
<td></td>
<td>Dose</td>
<td>Assess impact</td>
</tr>
<tr>
<td></td>
<td>Biomarker</td>
<td>Minimise risks</td>
</tr>
<tr>
<td></td>
<td>Drug interactions</td>
<td>Create awareness</td>
</tr>
<tr>
<td></td>
<td>Other</td>
<td>General description</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No action</td>
</tr>
</tbody>
</table>

Conclusions and perspective

• **Structured benefit-risk assessment** and communication now established; improvements possible
  - Developing a framework to enable **more systematic approach to uncertainties** and coping strategies
• Role of **quantitative approaches still unclear** for reviewers
  - But **companies encouraged to explore** quantitative methods (may help communicating)
• More systematic patient involvement
  - **Patient preference studies** may play a larger role in the future if we can refine the “toolkit”
Thank you

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Public Meeting on Benefit-Risk Framework Implementation

Swissmedic perspective on implementing benefit-risk assessment approaches to support drug development and evaluation

Claus Bolte, MD MBA – Sector Head Marketing Authorization
- **Purpose**
  - Decision
  - Documentation
  - Communicate (audience?)
- **Attempts to advance the concept**
  - Format (quantify?)
  - Therapeutic Area, (Sub-)Population
  - Application type
- **Outlook**
  - Patient preferences
  - PROs, QoL
  - Fact Box
  - Lifecycle approach
  - (Cost)

---

**Outline & Context**

**Summary**

The current situation of the biomedical sciences is critically discussed. It can be summarized as follows:

1. We have to acknowledge the presence of a serious credibility problem, which might undermine the foundations of medical science. ("Sliding on a slippery slope")
2. Multiple forces going beyond simple conflicts of interest push medical science further down the slippery slope. ("Who is pushing?")
3. The public awareness of something seriously wrong with medical science is mounting on all levels of our multimedia society. ("Looking into the media mirror")
4. Technical corrective measures may be easily implemented, however, to change an expanding and "successful" science culture actually destroying it's own foundations will need a sustained effort by the medical and scientific community on all levels. ("Look away - or act?")

**Key words:** biomedical science; irreproducibility; publication bias; ethical blindness; scientific integrity

Examples of potential COIs in medical research are:
- Patient care vs doctor / clinical researcher as agent for research;
- Scientific truth vs career opportunities (publication numbers, impact factors, university rankings);
- Science vs marketing (pharma, doctors, publishers);
- Healthcare system costs vs income/expenses of doctors, hospitals, cantons, pharma, insurance.

The common denominator is that a third party is at risk.
Interconnected world – post-trust Society

Social Media & Transparency

Empowered patients

Medical need grows faster than healthcare budgets

Personalized, Stratified, Precision Medicine

New facilitated (expedited) licensing pathways

New trial designs; RCT : RWD

Master protocols, basket trials

HTA (NICE, IQWiG, etc.), cost-benefit analyses

Pediatric (& Geriatric) Data

Data Exclusivity
When describing the benefit-risk assessment, the following additional aspects should be considered:

- The impact of the therapeutic context on the assessment, which may include information on the patient perspective if available. This discussion should consist of the following:
  - how the severity of disease and expected benefit influence the acceptability of the risks of the therapy.
  - how the medicinal product addresses a medical need.
- Key aspects of risk management that are important in reaching a favourable benefit-risk assessment, such as:
  - the proposed labeling.
  - whether non-responders can be readily identified allowing them to discontinue treatment.
  - other risk management activities, such as registries or restricted distribution systems.

There are many approaches available for conducting the benefit-risk assessment. This guideline does not prescribe a specific approach. A descriptive approach that explicitly communicates the interpretation of the data and the benefit-risk assessment will generally be adequate. An applicant may choose to use methods that quantitatively express the underlying judgments and uncertainties in the assessment. Analyses that compare and/or weigh benefits and risks using the submitted evidence may be presented. However, before using any method,
5. Guidance for Preparation of Clinical Assessment Reports (AR)

5.1 Guiding Principles and Key Objectives

Clinical Assessment Reports are a key tool to help make the clinical assessment process efficient, and to facilitate a transparent decision making process. The AR is the written documentation of the thoroughness of the clinical review, the benefit-risk assessment and decision making process. For this reason, the ARs are kept on file.

5.1.1 Purposes of AR

Assessment reports facilitate Swissmedic internal discussions, consensus finding and decision making during the clinical assessment process:

- The ARs help all parties involved (see section 5.1.3.) in the decision-making process to understand what are the issues which need to be discussed.
- The report should cover in sufficient detail the essential data from the submitted documentation to facilitate internal discussion of critical aspects and issues during the Peer Review process and Case Team (CT) discussion. Peer Review is of critical importance to ensure that the decisions captured in the Assessment Report are not a single-reviewer opinion but express the position of the Institute.
- The safety data presented in the AR should assist the Drug Safety CR (AMS-CR) in their review of the risk management plan (RMP). Class effects and any potential safety issues are to be identified.

- Authorisation does not mean that a drug cannot harm an individual patient
- Authorisation does not mean that an individual patient will necessarily experience benefit
- Authorisation should mean that, on a population basis, the potential risks (or level of uncertainty) are judged to be acceptable given the specific conditions of use, the target population and the alternatives available at the time of approval.
Figure 3: Number of NAS approvals by review type for six regulatory authorities in 2011-2015

*Expedited review* refers to EMA ‘Accelerated Assessment’ and FDA/PMDA ‘Priority Review’.

**TGA does not currently have an expedited evaluation program***

11% of the NASs approved in 2015 by Swissmedic were approved by Swissmedic first or within one month of their first approval at FDA, EMA, PMDA, Health Canada or TGA.
Summary and Proforma Template for the Benefit-Risk Assessment of Medicines

Professor Stuart Walker, Founder, Dr Neil McAuslane, Director, Centre for Innovation in Regulatory Science

User Manual

Please complete a new form for each indication. Please complete the proforma which will auto-populate the Summary. The sections in the proforma that populate the summary are highlighted in green. It has been decided for this pilot that the summary can only be completed via the proforma.

All data will be treated in strict confidence. No data or information will be revealed to any third party.

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<td>Human Pharmacology</td>
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<td>Clinical Summary</td>
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<td>Section 3</td>
<td>Identified Benefits and Risks</td>
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<td>3.1</td>
<td>List of all Benefits as Documented</td>
</tr>
<tr>
<td>3.2</td>
<td>List of all Risks as Documented</td>
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<tr>
<td>Section 4</td>
<td>Benefit-Risk - Study Information</td>
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<td>4.1</td>
<td>Benefits observed in pivotal and non-pivotal studies</td>
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<td>4.2</td>
<td>Risks Overall Summary</td>
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<td>4.3</td>
<td>Adverse Effects/Events</td>
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<td>Uncertainties (Benefits &amp; Risks)</td>
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<td>Benefit-Risk Summary Table &amp; Expert Judgment</td>
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<td>5.2</td>
<td>Risks - Weighting and Valuing</td>
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<td>Section 6</td>
<td>Visualisation</td>
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Benefit-Risk Summary Section

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<th>Section 8</th>
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<td>8.1</td>
<td>Benefit-Risk Conclusion</td>
</tr>
<tr>
<td>8.2</td>
<td>Decision Context</td>
</tr>
<tr>
<td>8.3</td>
<td>Identified Benefits and Risks</td>
</tr>
<tr>
<td>8.4</td>
<td>Benefit-Risk Weighting and Valuing</td>
</tr>
<tr>
<td>8.5</td>
<td>Benefit-Risk Management</td>
</tr>
</tbody>
</table>
### 2.5 If applicable: Paediatric Investigation Plan (PIP)

### 2.6 Assessment 1

#### 2.6.1 Preliminary Benefit-Risk Assessment

Not all submitted data have equal importance to the critical assessment of benefits and risk. It is acceptable to give preferential attention to the key elements and summarize other data by means of a short description.

The tabular Benefit-Risk Framework below is meant as a tool in the decision making process, it is not meant to replace free text descriptions of the benefit risk assessment.

- The utility of the Framework needs to be determined from case to case.
- The Framework is meant as an aid and mental map to make the assessments more structured and more systematic, the tool cannot replace judgment.
- The Framework should aid the reader of the report to get an efficient overview and summary what were the key data, uncertainties, their interpretation and conclusions from all five dimensions which are driving the benefit-risk assessment.

Refer also to Appendix 3 for further explanations about this Benefit-Risk Framework.

<table>
<thead>
<tr>
<th>Decision Factor</th>
<th>Evidence and Uncertainties</th>
<th>Conclusions and Reasons</th>
</tr>
</thead>
<tbody>
<tr>
<td>Analysis of Condition</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current Treatment Options</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Benefit</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Risk</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Risk Management</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Benefit Risk Summary Assessment</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Evidence

<table>
<thead>
<tr>
<th>Dose finding (CPR)</th>
<th>DCV + pegIFNα/RBV but not for DCV in combination with SOF</th>
<th>DCV + SOF</th>
<th>Acceptable since DCV/SOF is efficacious and safe.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interaction potential (CPR)</td>
<td>Extensive DDI study program</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| Pivotal study AI444040 with DCV/SOF (CR) | Positive: multi-center, randomized subjects which failed prior TCV/BOC treatment were included; high baseline HCV viral load; The chosen endpoints (SVR12 / 24) are according to the draft guideline EMEA/CHMP/51240/2011; high baseline HCV viral load; Presented efficacy data are compelling | Negative: Exploratory study; post-hoc statistical analysis plan; post-hoc data pooling of treatment groups; Exploratory phase 2 study with 10 treatment groups (n = 14 to 41 subjects); limited size; no cirrhosis patients which might benefit most from an IFN-free treatment; no confirmatory study | In general, single pivotal study meets the POINTS TO CONSIDER ON APPLICATION WITH 1. META-ANALYSES; 2. ONE PIVOTAL STUDY (CPMP/EWP/2330/99). Despite there is no confirmatory study for DCV/SOF, similar effects were demonstrated in different pre-specified sub-populations. All-important endpoints showing similar findings → acceptable despite limitations. Not all proposed sub-indications are reflected by the study population |

| Clinical safety (CR) | DCV/SOF: most frequently reported (≥ 10%) treatment-related AEs were fatigue, headache, and nausea. No Grade 3/4 treatment-related AEs were reported. DCV/SOF/RBV: Grade 1-2 AEs↑↑; hemoglobin laboratory abnormalities↑↑. Treatment-related AEs (any grade) were similar between pegIFNα/RBV ± DCV. No death were reported on treatment with DCV. | HIV/HCV | No unexpected AEs → acceptable safety profile |
|                      | In dogs bone marrow toxicity at 9-fold the clinical AUC. | HBV/HCV | PK: hepatic impairment → AUC↓ |
|                      | Hepatic and adrenal gland effects at exposures similar to clinical AUC. | Hepatic impairment and decompensated liver disease | PK: renal impairment → AUC↑ |
|                      | No safety signals in humans | Liver transplant | PK: BMI no significant effect |
|                      | Patients >65 years | | |

<table>
<thead>
<tr>
<th>Pre-clinical safety data (PCR)</th>
<th>Hepatic and adrenal gland effects at exposures similar to clinical AUC.</th>
<th>No safety signals in humans</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>DCV/SOF</th>
<th>GT-1, treatment naïve w/o cirrhosis</th>
<th>limitations of the pivotal phase 2 study but compelling results: (+)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>GT-1, TVR/BOC treatment failure</td>
<td>24 weeks R: (+)</td>
</tr>
<tr>
<td></td>
<td>12 weeks R: (-)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>GT-1, compensated cirrhosis</td>
<td>very limited clinical data → B/R assessment is not possible: (-)</td>
</tr>
<tr>
<td></td>
<td>GT-3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>GT-4</td>
<td></td>
</tr>
<tr>
<td></td>
<td>GT-4</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>DCV/pegIFNα/ RBV</th>
<th>GT-1</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>GT-3</td>
</tr>
<tr>
<td></td>
<td>GT-4</td>
</tr>
</tbody>
</table>

|                  | GT-4 | pivotal phase 3 study supports proposed indication: (+) |
How new fact boxes are explaining medical risk to millions

Smart “fact boxes” that communicate evidence based information on the benefits and harms of drugs and health screening are being rolled out to millions of people in Europe. Gerd Gigerenzer and Kai Kolpatzik report

Gerd Gigerenzer director1, Kai Kolpatzik head2

1 Harding Center for Risk Literacy and Center for Adaptive Behavior and Cognition, Max Planck Institute for Human Development, Berlin, Germany;
2 Department of Prevention, General Local Health Insurance Fund (AOK-Bundesverband), Berlin, Germany; Correspondence to: G Gigerenzer gigerenzer@mpib-berlin.mpg.de

An alien investigating healthcare on Earth would be quite puzzled. We spend billions on clinical studies but fail to ensure that patients and physicians are communicated the results transparently. Instead they get persuasion, marketing, and, in some countries, misleading direct-to-consumer advertising.
Market Access = Regulatory + HTA
<table>
<thead>
<tr>
<th>Target Audience</th>
<th>ASCO Value Framework</th>
<th>NCCN Value Pathways</th>
<th>ESMO MCB Scale</th>
<th>ICER Value Assessment</th>
<th>MSKCC DrugAbacus</th>
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</thead>
<tbody>
<tr>
<td>Evidence</td>
<td>Pivotal trials</td>
<td>Broad</td>
<td>Mainly phase II and III comparative trials</td>
<td>Broad</td>
<td>Pivotal trials</td>
</tr>
<tr>
<td>Efficacy</td>
<td>OS, PFS, RR, TFS</td>
<td>OS, PFS</td>
<td>OS, PFS</td>
<td>Varies; usually QALYs</td>
<td>OS</td>
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<td>Indirect Loss</td>
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<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>(Productivity)</td>
<td></td>
<td></td>
<td></td>
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<td>Toxicity</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<td>QOL/Palliation</td>
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<td>No</td>
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<td>No</td>
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<td>Patient Preference</td>
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<td>Cost</td>
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<td>Drug copay</td>
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<td>No</td>
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<td>New</td>
<td>New</td>
<td>New</td>
<td>New and old</td>
<td>New</td>
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<tr>
<td>Outcome</td>
<td>Net health benefit scale (20–130), drug cost</td>
<td>Score 1–5 on each of five evidence blocks</td>
<td>Graded 1–4</td>
<td>Value-based price</td>
<td>Value-based price</td>
</tr>
<tr>
<td>Use of Real-World Data</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Patient Perspective</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

Abbreviations: NCCN, National Comprehensive Cancer Network; ESMO, European Society for Medical Oncology; MCB, magnitude of clinical benefit; ICER, Institute for Clinical and Economic Review; MSKCC, Memorial Sloan Kettering Cancer Center; OS, overall survival; PFS, progression-free survival; RR, relative risk; QALY, quality-adjusted life-year; QOL, quality of life; TFS, treatment-free survival.
FDA Public Meeting on Benefit-Risk Framework Implementation

Silver Spring, MD
September 18, 2017

Tarek A. Hammad, MD, PhD, MSc, MS, FISPE
Head of Signal Detection and Benefit Risk Assessment
Disclaimer

- The views expressed in this talk are those of the presenter.

- I am giving this talk as a private individual and not as an affiliate with an employer, and as such, the principles, ideas, and perspectives provided during the talk are my own and not necessarily those of my employer.
Outline

1. Context of BR Evaluation in Drug Development

2. Challenges With Quantitative Approaches

3. Dimensions of Patient Engagement in Drug Development
The Benefit-Risk (BR) Balance: Context Matters

**Global context, eg:**
1. Disease (indication) severity
2. Expected extent of use
3. Available alternatives
4. Background rate of AE

**Public health interest**

**Local context, eg:**
1. Biological plausibility
2. Evidence for causality
3. Magnitude of harm
4. Severity/prognosis of AE
5. Can the risk be mitigated?

**Quality of evidence**

**Potential driven actions**
1. Not approved or complete response
2. Labeling and other regulatory actions
3. Request more studies premarket or postmarket
4. Risk communication and/or REMS (RMP)

**Remaining unknowns, eg:**
1. Potential latent risk
2. Subgroups of interest

**Totality of evidence (to date)**

**Local context, eg:**
1. Extent of benefit
2. Studied patient population (inclusions and exclusions)

**Disease (indication) severity**

**Expected extent of use**

**Available alternatives**

**Background rate of AE**

**Biological plausibility**

**Evidence for causality**

**Magnitude of harm**

**Severity/prognosis of AE**

**Can the risk be mitigated?**

**Extent of benefit**

**Studied patient population (inclusions and exclusions)**

**Potential latent risk**

**Subgroups of interest**

**Not approved or complete response**

**Labeling and other regulatory actions**

**Request more studies premarket or postmarket**

**Risk communication and/or REMS (RMP)**
"The best way to predict your future is to create it!"

Abraham Lincoln
The 16th President of the United States, 1861
1. Utilization of findings beyond traditional “primary study endpoints” (secondary and exploratory endpoints, eg convenience or PRO QoL)

2. Information about the patient perspective may be considered:
   • May be obtained directly from patients or indirectly from other stakeholders (eg, parents and caregivers) using qualitative, quantitative, or descriptive methods

3. An applicant may choose to use methods that quantitatively express the underlying judgments and uncertainties in the assessment. Analyses that compare and/or weigh benefits and risks using the submitted evidence may be presented

4. Written to be consistent with regulatory post-marketing requirements (eg, PBRER); creates a continuity
Outline

1. Context of BR Evaluation in Drug Development
2. Challenges With Quantitative Approaches
3. Dimensions of Patient Engagement in Drug Development
Logical Components of Evaluating BR Profiles

Identify key benefits and risks

Benefit-risk assessment
Logical Components of Evaluating BR Profiles

1. Identify benefits and risks
2. Benefit-risk assessment
3. Weigh benefits and risks
4. Characterize BR profile: tabulation, visualization

Explicit or implicit benefit-risk assessment

Quantitative metrics
Quantitative assessments

Benefit-risk assessment
Weighing of Benefits and Risks Can Be Explicit or Implicit...

What does “explicit” weighing entail?
The Age-Old Question...

Qualitative vs Quantitative Assessments
Quantitative Metrics vs Quantitative Assessments

Data collection

Identification of benefits and risks

Benefit-risk assessment

Descriptive/analytic

Complex modeling

Applying "value" judgment, no quantitative metrics (eg, value of A1C vs hypoglycemia)

Applying judgment using quantitative metrics (eg, RD, RR, NNT, NNH), no weighing of events with utilities/trade-offs

Applying judgment, weighing involved – utilities/trade-offs, eg, NCB MCDA, SMAA, DCE, BRR (quantitative assessments)

“Semi-quantitative” approach

Quantitative approach

Explicit

Data collection

Identification of benefits and risks

Benefit-risk assessment

Descriptive/analytic

Complex modeling

Applying "value" judgment, no quantitative metrics (eg, value of A1C vs hypoglycemia)

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“Semi-quantitative” approach

Quantitative approach

Explicit
Methodological Issues to Resolve

- What to do with prematurely terminated trials because of overt efficacy? Should BR profile be the endpoint?

- How substantial must a risk be to trigger revision of BR balance? (threshold discussion)

- What is the realistic role of quantitative approaches in BR assessment (e.g., MCDA, SMAA)?

- How can the patient have a say in the evaluation as emerging evidence accrues?
  - How can information be communicated to patients and healthcare providers (format, basis, frequency)?

- Accurate depiction of true levels of benefits and risks

- Specific challenges for new, breakthrough, or orphan drugs:
  - Paucity of information at the time of approval
  - Lack of widespread use limits the ability to collect information in the postmarket phase
Outline

1. Context of BR Evaluation in Drug Development
2. Challenges With Quantitative Approaches
3. Dimensions of Patient Engagement in Drug Development
Need Vocabulary Control

- Patient Involvement
- Patient Activation
- Patient Autonomy
- Patient Input
- Patient-Inspired Data
- Patient Preference
- Patient-Centered Approaches
- Patient Knowledge
- Patient Choices
- Patient Health Literacy
- Patient Perspective
- Patient Empowerment
- Patient-Related Drug Development
- Patient-Centeredness
- Patient Focus
- Patient Empowerment
- Patient Engagement
Dimensions of Patient Engagement in Product Development: Perspectives vs Preferences vs Choices

What is missing?

A) Patient preference (trade-offs, benefits vs harms):
   - Identify attributes of preference-sensitive scenarios
   - Capture at pertinent disease and life milestones (who, what, when, and how)
   - Integrate in the decision-making process at the time of approval, not after the fact (needs regulatory pathway)
   - Anticipate in prospective patients

B) Enhance patient understanding of BR balance (by evidence-based communication)

C) Empower patient choice by ensuring access to patient assistance and medication management services as well as evidence on comparative patient-focused outcomes

It Helps To Know What We Are Trying to Do: Should We Redefine Our Targets?

Patient Population

Maximize the benefit for patients while offering more choices

BR balance on average is positive

- Some use clinical phenotyping: finding different sub-types of diseases
- Help characterize patient preference

Find predictors that help characterize patient preference

Find predictors that help characterize patient response to ttt

Premise
Objective??
Implication
Challenge

*https://www.youtube.com/watch?v=MKiw7yAqqsU
In Conclusion...

• The complexity of the decision-making process in BR assessment dictates the need for a structured approach

• Need to identify and address knowledge gaps, while minding the scientific boundaries of our tools

• Need for a better way to truly characterize and incorporate pertinent patients’ prospective in drug development

• It is not clear what is the appropriate timing in the development lifecycle to discuss BR framework/quantitative plans with the agency (eg EOPII? Earlier?)

• For this field to advance, regulators should provide targeted feedback on the contribution of quantitative BR evidence to the overall decision
Benefit-Risk Assessment in Drug Development: Progress to Date and Future Directions

Rebecca Noel, DrPH, MSPH
PhRMA Deputy Lead M4E(R2)
Global Benefit-Risk Leader
Eli Lilly and Company
Disclaimer

Becky Noel is an employee and shareholder of Eli Lilly and Company. The views and opinions represented in this presentation are solely hers and are not intended to represent the views and opinions of Eli Lilly and Company.
Benefit and Risk: Pillars of Regulatory Decision-Making

To be approved for marketing, a drug must be safe and effective for its intended use...

- The meaning of “safe” is not explicitly defined in the statutes or regulations that govern approvals
- Recognizing all drugs have some ability to cause adverse effects, safety is assessed by determining whether its benefits outweigh its risks
- This benefit-risk assessment is the basis of pre-market and post-market regulatory decisions
So What Can Make Benefit-Risk Decision Making Challenging?

There are many factors that can make a decision challenging:

- Lack of clarity
- Complexity
- Lack of certainty
- Conflicting objectives
- Lack of structure
- Inappropriate frame
- Lack of judgment criteria
- “What’s on the Regulator’s Mind”

What’s On The Regulator’s Mind?

- Adverse Event Incidence
- Availability of Other Therapies
- Restricted Distribution
- Target Population
- Communication
- Treatment Effect
- Risk Management
- Medication Guides
- Trial Design and Conduct
- Nature of Disease
- Study Population
- Education
- Risk of Products In Same Class
- Trial Drop-outs
- Statistical Significance
- Labeling
- Clinical Relevance Of Endpoint
- Serious Adverse Event Incidence
- Relative Efficacy
- Expected Patient Compliance
- Off-Label Potential
- Risk in Chronic Use
- Patient Preference
- Efficacy in Subgroups
- Uncertainty
So What is a Higher “Quality Decision”?  

Shouldn’t confuse OUTCOMES with DECISIONS  
- It is human nature to want to judge a decision by the outcome, but….
  - Good decisions can have bad outcomes
  - Bad decisions can have good outcomes

Instead, decision quality should be judged by the PROCESS by which the decision was made…suggesting the need for a decision FRAMEWORK!
## FDA Benefit-Risk Framework

<table>
<thead>
<tr>
<th>Decision Factor</th>
<th>Evidence and Uncertainties</th>
<th>Conclusions and Reasons</th>
</tr>
</thead>
<tbody>
<tr>
<td>Analysis of Condition</td>
<td></td>
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<tr>
<td>Current Treatment Options</td>
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<tr>
<td>Risk Management</td>
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</tbody>
</table>

### Decision Context

### Benefit and Risk Attributes

### Benefit-Risk Optimization

### Benefit-Risk Summary Assessment

#### Decision Factors
1. Analysis of condition
2. Current treatment options
3. Benefit
4. Risk
5. Risk management

#### Levels of consideration
1. Evidence and uncertainties
2. Conclusions and reasons

#### Summary
- Benefit-risk summary assessment
B-RA Frameworks: Support for Decision-Making and Communication

### FDA

<table>
<thead>
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**Benefit-Risk Summary Assessment**

### EMA

**Favourable effects**

**Uncertainty of favourable effects**

**Unfavourable effects**

**Uncertainty of unfavourable effects**

### PhRMA BRAT

**Table 1 Steps in applying the BRAT Framework**

<table>
<thead>
<tr>
<th>Step</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Define the decision context</td>
<td>Define drug, dose, formulation, indication, patient population, comparator(s), time horizons for outcomes, perspective of the decision makers (regulator, sponsor, patient, or physician)</td>
</tr>
<tr>
<td>2. Identify outcomes</td>
<td>Select all important outcomes and create the initial value tree. Define a preliminary set of outcome measures/endpoint points for each. Document rationale for outcomes included/excluded.</td>
</tr>
<tr>
<td>3. Identify and extract source data</td>
<td>Determine and document all data sources (e.g., clinical trials, observational studies). Extract all relevant data for the data source table, including detailed references and any annotations, to help the subsequent interpretations create summary measures.</td>
</tr>
<tr>
<td>4. Customize the framework</td>
<td>Modify the value tree on the basis of further review of the data and clinical expertise. Refine the outcome measures/endpoint points. May include tuning of outcomes not considered relevant to a particular benefit-risk assessment or that vary in relevance by stakeholder group.</td>
</tr>
<tr>
<td>5. Assess outcome importance</td>
<td>Apply or assess any ranking or weighting of outcome importance to decision makers or other stakeholders.</td>
</tr>
</tbody>
</table>
So Which Framework?: Global Guidance Begins to Emerge

International Council on Harmonization (ICH): Revision of M4E Guideline Enhancing the Format and Structure of Benefit-Risk Information in ICH
The Clinical Overview provides a critical analysis of the clinical data in the Common Technical Document.

- Accomplished by referring to:
  - Application data provided in the comprehensive Clinical Summary
  - Individual clinical study reports
  - Other relevant reports
The Challenge to Critical Thought

• Tyranny of the “Summary of the Summary” in the CO and beyond
  • Need to promote critical analysis, rather than relying on the dreaded summary of the summary
  • A challenge not only for industry but also for regulators implementing their processes at the reviewer level
    ➢ Still a threat, even with the ICH update and FDA framework!

• So the question for industry and regulators alike is, how do we use the excellent gains we’ve made through PDUFA V, VI and ICH to move further?
Supporting Critical Analysis: What Do We Need?

1) Developing Section 2.5.6 and beyond
   ✓ Expectations for what good looks like?
   ✓ How do we get there?

2) Capacity building
   ✓ Developing benefit-risk application experience & tools
   ✓ Understanding and using quality decision-making

3) Collaboration and connection
Section 2.5.6 Guidance: ICH Questions & Answers Document

• No Q&A document at this time
  • Expert Working Group consensus: industry and regulators would benefit from ‘living with’ M4E(R2) for a short interval to better identify whether questions exist that are best addressed through an ICH Q&A document
  • No change in this position since EWG concluded in 2016

SO…Section 2.5.6 update provides the WHAT (remember….‘Format & Structure’), but still faced with the HOW?
No ICH Q&A Document...So How Do We Know What Good Looks Like?

Mutual, increased clarity on what good looks like … …supports the likelihood of success!

- FDA Guidance in 2020: use FDA reviewer guidance in collaboration with industry and patients to elaborate what good looks like and how to achieve it
- Since continued development of benefit-risk should occur in a precompetitive, cooperative manner, suggest a public-private partnership to jointly address methodological and practice related issues, best practices for industry, regulators and patients
  - MDIC offers a positive model!
## Capacity Building: Realizing PDUFA V&VI Benefit-Risk Goals

### Progress the FDA framework

- Advance the baseline
  - Broader use in dialoguing with the Agency and eventually, patients
  - Greater transparency on how decisions are made
- Data summarization and visualizations supportive of the decision are critical addition
- Methods tool kit or catalog
- Standards for methods application
- Assessing outcome importance
- Adaptation and application to post-marketing assessments

### Use of patient perspective methods in benefit-risk assessment, with inclusion in labeling as a tool for patient communication

- Resolve how partially completed patient perspective information (Voice of the Patient snapshots) can be updated and used in reviews
- Use and communication of patient developed perspectives submitted directly to the Agency
- Types of data and how FDA will evaluate it

### Qualitative and Quantitative benefit-risk assessment

- Develop a methods catalog with standards, best practices
• Build knowledge and experience not only with preferences, statistics, and methods but also with areas such as ‘Quality Decision Making’ and ‘Judgment Based Decision Making’, which give insight into the principles and processes of qualitative and quantitative benefit-risk assessment
  ✓ Practical constructs based on the theory and practice of Decision Sciences
MOON SHOT
Moon Shot Thinking: Integrated Benefit-Risk Science

What’s Needed Here?: Connection, Collaboration, and Communication

<table>
<thead>
<tr>
<th>RWE &amp; Big Data</th>
<th>Patient Focused Drug Development</th>
<th>Methods &amp; Tools</th>
<th>Training and Education</th>
<th>Policy and Regulatory Science</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active surveillance and connecting risk data into B-R</td>
<td>Developing and applying patient perspectives in regulatory review &amp; development</td>
<td>Software tools</td>
<td>Common training for FDA reviewers, industry, patients</td>
<td>Inclusion of B-R in labeling</td>
</tr>
<tr>
<td>Improved effectiveness data with benefits evidence</td>
<td>Disease perspective guidelines</td>
<td>Framework progression</td>
<td>Treatment of uncertainty</td>
<td>Collaboratively developed Guidances</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Treatment of uncertainty</td>
<td></td>
<td>Use beyond review: Application across the lifecycle</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Fit for purpose qualitative &amp; quantitative methods</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Current or ‘Blue Sky’ Activities
Session 1
Panel Discussion and Q&A

Graham Thompson
Facilitator

September 18, 2017
LUNCH
Session 2
Approaches to Incorporating Patient Perspectives into Benefit-Risk Assessment

Pujita Vaidya
Facilitator

September 18, 2017
Informing Benefit-Risk Assessment With Patients’ Perspective:

FDA Patient-Focused Drug Development

Theresa Mullin, Ph.D.
Director, Office of Strategic Programs
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

September 18, 2017
FDA Approach to Benefit-Risk

– Qualitative approach that is grounded in quantification of various data elements. 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)

– Evaluation of B-R is dynamic
  • Knowledge of benefits and risks evolves over product life-cycle

– Decisions on B-R require judgment on the part of the regulator and are influenced by:
  • Statutory/regulatory standards
  • Societal expectations
  • Personal values and perspectives
### Patient Perspective Can Inform BR Assessment at Multiple Levels

#### Benefit-Risk Summary and Assessment

<table>
<thead>
<tr>
<th>Dimension</th>
<th>Evidence and Uncertainties</th>
<th>Conclusions and Reasons</th>
</tr>
</thead>
<tbody>
<tr>
<td>Analysis of Condition</td>
<td>Patient Focused Drug Development</td>
<td>Patient Focused Drug Development</td>
</tr>
<tr>
<td>Current Treatment Options</td>
<td>Provides the therapeutic context for weighing benefits and risks</td>
<td>Provides the therapeutic context for weighing benefits and risks</td>
</tr>
<tr>
<td>Benefit</td>
<td>Clinical Outcome Assessments (e.g., PROs)</td>
<td>Clinical Outcome Assessments (e.g., PROs)</td>
</tr>
<tr>
<td>Risk</td>
<td>Incorporates expert judgments about the evidence of efficacy and safety, and efforts to further understand or mitigate risk</td>
<td>Incorporates expert judgments about the evidence of efficacy and safety, and efforts to further understand or mitigate risk</td>
</tr>
<tr>
<td>Risk Management</td>
<td></td>
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</tr>
</tbody>
</table>
Patient-Focused Drug Development

• Patients are uniquely positioned to inform FDA understanding of the clinical context

• FDA could benefit from a more systematic method of obtaining patients’ point of view on the severity of a condition, its impact on daily life, and their assessments of available treatment options
  – Current mechanisms for obtaining patient input are often limited to discussions related to specific applications under review, such as Advisory Committee meetings

• Patient-Focused Drug Development initiative offered a more systematic way of gathering patient perspective on their condition and treatment options
  – FDA committed to convene at least 20 meetings on specific disease areas over the next five years
  – Meetings help advance a systematic approach to gathering input
Commitment in PDUFA V:
Patient-focused drug development meetings
incorporating patient’s voice to decision making

Plan to complete 24 meetings during PDUFA V

<table>
<thead>
<tr>
<th>Fiscal Year 2013</th>
<th>Fiscal Year 2014</th>
<th>Fiscal Year 2015</th>
<th>Fiscal Year 2016</th>
<th>Fiscal Year 2017</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Chronic fatigue syndrome/myalgic encephalomyelitis</td>
<td>• Sickle cell disease</td>
<td>• Female sexual dysfunction</td>
<td>• Non-tuberculous mycobacterial lung infections</td>
<td>• Sarcopenia</td>
</tr>
<tr>
<td>• HIV</td>
<td>• Fibromyalgia</td>
<td>• Breast cancer</td>
<td>• Psoriasis</td>
<td>• Autism</td>
</tr>
<tr>
<td>• Lung cancer</td>
<td>• Pulmonary arterial hypertension</td>
<td>• Chagas disease</td>
<td>• Neuropathic pain associated with peripheral neuropathy</td>
<td>• Alopecia areata</td>
</tr>
<tr>
<td>• Narcolepsy</td>
<td>• Inborn errors of metabolism</td>
<td>• Functional gastrointestinal disorders</td>
<td>• Patients who have received an organ transplant</td>
<td>• Hereditary angioedema (September 25)</td>
</tr>
<tr>
<td></td>
<td>• Hemophilia A, B, and other heritable bleeding disorders</td>
<td>• Huntington’s disease and Parkinson’s disease</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## Participation Estimates

<table>
<thead>
<tr>
<th>In-Person</th>
<th>Registered</th>
<th>Attended</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient / Representatives</td>
<td>40 – 185</td>
<td>30 - 120</td>
</tr>
<tr>
<td>Other (e.g., NIH, industry)</td>
<td>40 – 115</td>
<td>30 - 140</td>
</tr>
<tr>
<td>Webcast</td>
<td>250 - 650</td>
<td>~50% of registered</td>
</tr>
<tr>
<td>Docket Submissions</td>
<td>5 - 400</td>
<td></td>
</tr>
</tbody>
</table>
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 in-person participants
  - Interactive webcast and phone line for remote participants
  - A federal docket allowing for more detailed comments
Burden of Disease

- Of all the symptoms that you experience because of your condition, which 1-3 symptoms have the most significant impact on your life?

- Are there specific activities that are important to you but that you cannot do at all or as fully as you would like because of your condition?

- How has your condition and its symptoms changed over time?

- What worries you most about your condition?
Burden of Treatment

• What are you currently doing to help treat your condition or its symptoms?

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

• What are the most significant downsides to your current treatments, and how do they affect your daily life?

• Assuming there is no complete cure for your condition, what specific things would you look for in an ideal treatment for your condition?
PFDD Outcomes

- Each meeting results in a **Voice of the Patient** report that faithfully captures patient input from the various information streams
  - May include a sample of the B-R Framework’s first two rows, incorporating meeting input

- This input can support FDA staff, e.g.:
  - Conducting B-R assessments for products under review
  - Advising drug sponsors on their drug development programs

- Input could support other aspects of drug development, e.g.
  - Help identify areas of unmet need
  - Develop clinical outcome tools (PROs, etc.) that better address patient needs
Externally-Led PFDD Meetings

• Substantial external interest in expanded efforts to gather patient input in support of drug development and evaluation

• Meetings conducted by external stakeholders provide an opportunity to expand the benefits of PFDD
  – Meetings can target disease areas where there is an identified need for patient input on topics related to drug development
  – FDA’s PFDD meetings can serve as a model

• FDA is open to participating in such meetings (held locally)

• Meeting success requires joint and aligned effort by all interested stakeholders

• [http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm453856.htm](http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm453856.htm)
Some PFDD Learnings to Date

• Patients with chronic serious disease are experts on what it’s like to live with their condition

• Patients “chief complaints” may not be factored explicitly into drug development plans, including measures of drug benefit planned in trials

• For progressive degenerative diseases many patients/parents feel an ideal treatment would at minimum stop progression of their/their child’s loss of function

• Patients want to be as active as possible in the work to develop and evaluate new treatments; they and caregivers are able and willing to engage via Internet, social media, and other means

PFDD was intended to elicit broader patient input for a disease to better inform clinical context of BR assessment—What’s next?
PFDD Next Steps

• Engage wider community to discuss methodologically sound approaches that:
  • Bridge from initial PFDD meetings to more systematic collection of patients’ input
  • Generate meaningful input on patients’ experiences and perspectives to inform drug development and B-R assessment
  • Are “fit for purpose” in drug development and regulatory context

• Provide guidance
  – For patient communities, researchers, and drug developers
  – On pragmatic and methodologically sound strategies, pathways, and methods to gather and use patient input
What methods and approaches might be helpful to address in guidance?

• Collecting comprehensive patient community input on burden of disease and current therapy
  – How to engage with patients to collect meaningful patient input?
  – What methodological considerations to address?

• Development of holistic set of impacts (e.g., burden of disease and burden of treatment) most important to patients
  – How to develop a set of impacts of the disease and treatment?
  – How to identify impacts that are most important to patients?

• Identifying and developing good measures for the identified set of impacts that can then be used in clinical trials.
  – How to best measure the impacts (e.g., endpoints, frequency, etc.) in a meaningful way?
  – How to identify measure(s) that matter most to patients?

• Incorporating measures (COAs) into endpoints considered significantly robust for regulatory decision making
  – Topics including technologies to support collection through analysis of the data
Further integrating patient perspective into drug development and decision making

What impacts (burden of disease and burden of treatment) matter most to patients and how to measure them?

What aspects of clinical trials can be better tailored to meet the patients who (might) participate in the trial?

How to better integrate patient reported outcome data or elicited patient preferences into Benefit-Risk (BR) assessments?

How to best communicate the information to patients and prescribers?
Incorporating Patient Preferences into Regulatory Benefit-Risk Assessment

Telba Irony, PhD
Deputy Director
Office of Biostatistics and Epidemiology
Center for Biologics Evaluation and Research
FDA - CBER

September 18, 2017
What does CBER regulate?

- Blood, Blood Components
- Blood Derivatives
- Cell Therapies
- Related Devices
- Therapeutic Probiotics
- Vaccines: Preventive & Therapeutic
- Xenotransplantation Products
- Tissues
- Gene Therapies
Center for Devices and Center for Biologics

Guidance for Industry and Food and Drug Administration Staff

Factors to Consider When Making Benefit-Risk Determinations in Medical Device Premarket Approval and De Novo Classifications

The draft of this document was issued on August 15, 2011.

As of October 23, 2016, this document supersedes “Factors to Consider When Making Benefit-Risk Determinations in Medical Device Premarket Approvals and De Novo Classifications” dated March 28, 2012.

For questions about this document concerning devices regulated by CDRH, contact the Office of the Center Director at 301-796-5900. For questions about this document concerning devices regulated by CBER, contact the Office of Communication, Outreach and Development (OCOD) by calling 800-835-4709 or 301-827-1800.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health
Center for Biologies Evaluation and Research
Factors for Benefit-Risk Determination

• **Benefits**: type, magnitude, probability, duration
• **Risks**: severities, types, probabilities, duration
  risk of false positives and false negatives: diagnostic devices

**Additional Factors: Context**

• Uncertainty
• Severity and chronicity of the disease
• Availability of alternative treatments
• **Patient tolerance for risk and perspective on benefit**
• Risk mitigation
• Post-market information
• Novel technology for unmet medical need
“Risk tolerance will vary among patients, and this will affect individual patient decisions as to whether the risks are acceptable in exchange for a probable benefit. ... FDA would consider evidence relating to patients’ perspective of what constitutes a meaningful benefit.”

The Benefit-Risk guidance did not say how to collect and submit Patient Preference Information (PPI)
Center for Devices’ Proof-of-Concept Study: Devices to Treat Obesity

• Explore how to elicit and incorporate patient preferences into regulatory decision making

• Device treatments for obesity involve difficult benefit-risk tradeoffs

• Broad array of devices in the pipeline with diverse benefit-risk profiles

• Assess feasibility of eliciting patient preferences

• Assess the use of quantitative patient preferences

• Explore the use of quantitative preference results in regulatory decision making
Which is a favorable Benefit-Risk tradeoff?

Risks

↓ Benefit

Diet, Exercise

↓ Risk

New Treatment

Weight Loss

Gastroplasty

Gastric Banding
Obesity Study

- Sample: ~650 subjects with BMI ≥ 30; willing to lose weight

Discrete-Choice Experiment (DCE)

- Respondents evaluate choices between pairs of hypothetical weight-loss device-treatments
- Each treatment is defined by its attributes and levels (including surgical procedure)
- The pattern of choices reveals the patients’ preferences
- Ex: Patients would tolerate 2 more months of mild Adverse Events to lose 25 more pounds
## Attributes and Levels: Obesity Study

<table>
<thead>
<tr>
<th>Attribute</th>
<th>Levels</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type of Operation</strong></td>
<td>Endoscopic</td>
</tr>
<tr>
<td></td>
<td>Laparoscopic</td>
</tr>
<tr>
<td></td>
<td>Open Surgery</td>
</tr>
<tr>
<td><strong>Diet restrictions</strong></td>
<td>Eat ¼ cup at a time</td>
</tr>
<tr>
<td></td>
<td>Wait 4 hours between eating</td>
</tr>
<tr>
<td></td>
<td>Can’t eat hard-to-digest foods</td>
</tr>
<tr>
<td><strong>Average weight-loss</strong></td>
<td>5% of body weight</td>
</tr>
<tr>
<td></td>
<td>10% of body weight</td>
</tr>
<tr>
<td></td>
<td>20% of body weight</td>
</tr>
<tr>
<td></td>
<td>30% of body weight</td>
</tr>
<tr>
<td><strong>How long weight-loss lasts</strong></td>
<td>6 months</td>
</tr>
<tr>
<td></td>
<td>1 year</td>
</tr>
<tr>
<td></td>
<td>5 years</td>
</tr>
<tr>
<td><strong>Comorbidity improvement</strong></td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>Reduce risk (or current dosage) by half</td>
</tr>
<tr>
<td></td>
<td>Eliminate risk (or current dosage)</td>
</tr>
</tbody>
</table>
### Attributes and Levels: Obesity Study

<table>
<thead>
<tr>
<th>Attribute</th>
<th>Levels</th>
</tr>
</thead>
</table>
| How long side effect lasts                          | None  
1 month  
1 year  
5 years                                           |
| Chance of serious Side Effects requiring hospitalization | None  
5% chance hospitalization, no surgery  
20% chance hospitalization., no surgery  
5% hospitalization for surgery                       |
| Chance of dying from getting weight-loss device     | None  
1%  
3%  
5%  
10%                                                  |
<table>
<thead>
<tr>
<th>Feature</th>
<th>Device A</th>
<th>Device B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of operation</td>
<td>Endoscopic surgery</td>
<td></td>
</tr>
<tr>
<td>Recommended diet restriction</td>
<td>Wait 4 hours between meals</td>
<td></td>
</tr>
<tr>
<td>On average, how much weight is lost</td>
<td>30 lbs.</td>
<td>60 lbs.</td>
</tr>
<tr>
<td>On average, how long the weight loss lasts</td>
<td>Weight loss lasts 5 years</td>
<td>Weight loss lasts 1 year</td>
</tr>
<tr>
<td>Average reduction in dose of prescription drugs</td>
<td>Eliminates the need</td>
<td></td>
</tr>
<tr>
<td>for diabetes at the lower weight</td>
<td>for prescription drug</td>
<td></td>
</tr>
<tr>
<td>On average, how long side effects last</td>
<td>Last 1 month</td>
<td>Last 1 year</td>
</tr>
<tr>
<td>(Remember that side effects will limit your</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ability to do daily activities several times a</td>
<td></td>
<td></td>
</tr>
<tr>
<td>month.)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chance of a side effect requiring hospitalization</td>
<td></td>
<td>None</td>
</tr>
<tr>
<td>Chance of dying from getting the weight loss</td>
<td><img src="10%25_out_of_100.png" alt="10%" /></td>
<td><img src="1%25_out_of_100.png" alt="1%" /></td>
</tr>
<tr>
<td>device</td>
<td>(10 out of 100)</td>
<td>(1 out of 100)</td>
</tr>
<tr>
<td>Which weight-loss device do you think is better</td>
<td><img src="Device_A.png" alt="Device A" /></td>
<td><img src="Device_B.png" alt="Device B" /></td>
</tr>
<tr>
<td>for people like you?</td>
<td>Device A</td>
<td>Device B</td>
</tr>
</tbody>
</table>
Results: Preference Weights

Better outcomes have significantly higher weights.
Results: Preference Weights

Mortality Risk, Weight Loss, and Weight-Loss Duration are the most important.
Decision Aid Tool

• Calculates the minimum benefit patients would require for a treatment with a given mortality risk and other attributes

• Calculates the maximum risk patients would accept for a treatment with given weight-loss benefit and other attributes

• Results reported for various levels, from risk averse to risk tolerant

• Calculates the proportion of patients who would choose to get the device instead of status quo

• The estimated values inform the determination of the “minimum clinically significant benefit” that will be used in the clinical trial design and analysis
Regulatory Impacts of the Obesity Study

- The study, published in 2015 (Surgical Endoscopy), quantifies patients’ values to help **define minimum clinically meaningful benefit**
- Method adaptable for other medical products
- DCE: Only one of existing preference elicitation methods
- Maestro System, a vagus nerve stimulator indicated for weight-loss, was approved on January 14, 2015: estimated 10% patients accepting the device was instrumental to its approval
- Helped develop the Patient Preference Info guidance document by CDRH & CBER (released in 2016)
- Motivated development of a project by Medical Device Innovation Consortium & CDRH (delivered 2015)
Impacts: Patient Preference Initiative

Incorporating patient-preference evidence into regulatory decision making

Martin P. Ho - Juan Manero-Gonzalez - Herbert P. Lasner -
Carolyn V. Neidanth - Joyce M. Whang - Michele McGary-Mathis -
A. Scott Marley - Tuba Isin

Received: 3 September 2014 Accepted: 9 November 2014
© Springer International Business Media New York Journal for the USA 2015

Abstract

Background: Patient preferences are unique to each individual and may influence their treatment options. Therefore, patient preferences should be considered in decision-making processes. Recent advances in patient-preference evidence have shown that patient preferences are important when determining the acceptability of medical devices.

Objective: To determine the impact of patient-preference evidence on regulatory decision-making.

Methods: A systematic review of patient-preference evidence was conducted. The evidence was evaluated using a scoring system to assess the strength of the evidence. The results were used to inform decision-making processes.

Results: The evidence supported the use of patient-preference evidence in decision-making processes. The results also highlighted the importance of patient involvement in the development of medical devices.

Conclusion: Patient-preference evidence is an important component of regulatory decision-making. The use of patient-preference evidence can improve patient outcomes and increase patient satisfaction.

MEDICAL DEVICE INNOVATION CONSORTIUM (MDIC) PATIENT CENTERED BENEFIT-RISK PROJECT REPORT:

A Framework for Incorporating Information on Patient Preferences Regarding Benefit and Risk into Regulatory Assessments of New Medical Technologies

Inhalation Ventilation Innovations

MDIC

For questions about this document regarding CDRH-regulated devices, contact the Office of Communication, Outreach, and Development (OCOD) at 1-800-852-8705 or via email at cib disruptions@fda.hhs.gov.

For questions about this document regarding CBER-regulated devices, contact the Office of Communications, Outreach, and Development (OCOD) at 1-800-852-8705 or via email at cib disruptions@fda.hhs.gov.
CBER’s Science of Patient Input (SPI) Initiative

What is SPI?

Scientifically valid, qualitative and quantitative methods for capturing patient perspective information (PROs and PPI) and for incorporating it into product review and regulatory decision-making.

PRO
Patient-Reported Outcomes
Measure concepts best known or only known by the patient (e.g. pain, fatigue)

PPI
Patient Preference Information
Measure preferences for benefit-risk tradeoffs
CBER’s SPI Initiative

- Supports Agency efforts to systematically capture and incorporate patient perspectives into the regulatory framework

- Advance SPI:
  - Build internal review capacity and expertise
  - Collaborate with our FDA colleagues and external stakeholders
  - Explore existing and new ways to integrate SPI information into the regulatory framework
  - Track our experience to inform continuous improvement of SPI efforts
Current CBER SPI Activities

• Clotting Factors Use in Hemophilia
  – Comparison of the results from stated-preference studies with RWE (clinical, PFDD, PK/PD model)

• Education and Training

• Assessment to understand the current role of patient input in CBER-regulated product reviews

• Review patient input studies
Example of Preference Sensitive Decision in CBER: Clotting Factors use in Hemophilia

Two treatments option

Prophylaxis dosage based on patient’s weight:
  • Requires no blood samples from patients
  • May need less infusions
  • Some patients have a higher risk of bleeding

Prophylaxis dosage adjusted according to PK-profile:
  • Requires blood samples for construction of PK-profile
  • May need more infusions (determined by PK-profile)
  • Adjusted PK-dosing may reduce bleeding risk
# Example of Preference Sensitive Decision

## Clotting Factors use in Hemophilia

<table>
<thead>
<tr>
<th>Attributes</th>
<th>Values</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Current Treatment</strong></td>
<td><strong>New Treatment</strong></td>
</tr>
<tr>
<td>Prophylaxis dosage based on patient body weight</td>
<td>Prophylaxis dosage adjusted to PK profile</td>
</tr>
<tr>
<td>1. Number of blood samples necessary to construct PK-profile</td>
<td>No PK-profile, so no blood samples</td>
</tr>
<tr>
<td></td>
<td>At 3 time points</td>
</tr>
<tr>
<td>2. Advised frequency of prophylactic infusions</td>
<td>Infusions 2-3 times/week</td>
</tr>
<tr>
<td></td>
<td>Infusions every other day</td>
</tr>
<tr>
<td>Su</td>
<td>X</td>
</tr>
<tr>
<td>Mo</td>
<td>X</td>
</tr>
<tr>
<td>Tu</td>
<td>X</td>
</tr>
<tr>
<td>We</td>
<td>X</td>
</tr>
<tr>
<td>Th</td>
<td>X</td>
</tr>
<tr>
<td>Fr</td>
<td>X</td>
</tr>
<tr>
<td>Sa</td>
<td>X</td>
</tr>
<tr>
<td>3. Frequency of repetitive PK-profiling</td>
<td>No construction of PK-profile</td>
</tr>
<tr>
<td></td>
<td>Every other year</td>
</tr>
<tr>
<td>4. Risk of bleeding</td>
<td>Current frequency of bleeding</td>
</tr>
<tr>
<td></td>
<td>Reduced frequency of bleeding</td>
</tr>
<tr>
<td>Which treatment would you choose?</td>
<td>□</td>
</tr>
<tr>
<td></td>
<td>□</td>
</tr>
</tbody>
</table>
Take away message

• Patient preference information is an important supplement to clinical and statistical evidence and can enhance benefit-risk assessments for regulatory decision making

• Evidence on patient preference can be scientifically obtained

• Patient preference information can provide insights to reviewers who may have very limited experience with rare disease patients

• The Science of Patient Input is evolving
Using Patient Input in Regulatory Decision Making at CDRH

Martin Ho, MS
Associate Director for Quantitative Innovations
Office of the Surveillance and Biometrics
Center for Devices and Radiological Health

September 18, 2017
Patients are at the Heart of What We Do

CDRH Vision: Patients in the U.S. have access to high-quality, safe, and effective medical devices of public health importance first in the world
Evolution of the Role of the Patient

Traditional Medicine:
Provider-led treatment decision-making

Emerging Diseases:
Patient advocacy for availability of and access to new treatments

The Internet:
Patient empowerment through information

The Future Today:
Patient-Provider partnership in treatment decision-making

www.fda.gov
Patient Input

• Patient input includes a wide range of information and perspectives
  – Anecdotal comments in correspondence to the FDA
  – Testimony at Advisory Committee Panel meetings
  – Patient opinions expressed publicly including through social media
  – Patient responses to qualitative *ad hoc* surveys
  – Quantitative measurements of patient-reported outcomes
Patient Perspectives

• Patient perspectives refer to a type of patient input
• Information relating to patients’ experiences with a disease or condition and its management
• May be useful for:
  – better understanding the disease or condition and its impact on patients
  – identifying outcomes most important to patients
  – understanding benefit-risk tradeoffs for treatment

www.fda.gov
Regulatory Impact

- Patient-Informed Needs
- Patient-Preferred Benefit-Risk Information
- Patient-Centered Outcomes
- Communicating Benefit-Risk Information to Patients

Development Phases:
- Discovery + Ideation
- Invention + Prototyping
- Pre-Clinical
- Clinical
- Regulatory Decision
- Product Launch
- Post-Market Monitoring

Patient-Informed Clinical Trial Design, Patient-Reported Outcomes

- Consistent with CDER’s Structural Framework
- Worksheet with questions to guide evaluation of each factor
- Patient Preference Information (PPI) as important factor:

<table>
<thead>
<tr>
<th>PPI Factors</th>
<th>Questions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient-Reported Outcomes</td>
<td>• Do benefit(s) and risk(s) include effects on patients’ health-related quality of life?</td>
</tr>
<tr>
<td>Benefit-Risk Considerations</td>
<td>• Which benefits and risks are most important to affected patients?</td>
</tr>
<tr>
<td></td>
<td>• What benefit-risk tradeoffs are acceptable from the patient perspective?</td>
</tr>
<tr>
<td></td>
<td>• Are there clinically-relevant subgroups of patients that would choose a particular benefit-risk profile over other alternatives?</td>
</tr>
<tr>
<td></td>
<td>• Does PPI capture diverse preference across the spectrum of indicated population and thus, generalizable?</td>
</tr>
</tbody>
</table>
We interact with patients as partners and work together to advance the development and evaluation of innovative devices, and monitor the performance of marketed devices.

1. Promote a culture of meaningful patient engagement by facilitating CDRH interaction with patients.

2. Increase use and transparency of patient input as evidence in our decision making.
Patient Engagement Advisory Committee

• To help assure the needs and experiences of patients are incorporated into our work, the PEAC will:

  1. Advise CDRH on ways to include and foster participation of patients where appropriate throughout the total product lifecycle
  2. Advise CDRH on patient perspectives about current and new approaches or policies for integrating patient input in regulatory decision-making
  3. Serve as a resource to CDRH as a body of experts in patient experience, needs, and the activities of the patient community

• Inaugural Meeting is October 11-12, 2017

CDRH Commits to Science of Patient Input

- First patient-centric commitments in MDUFA’s history
- Build capacity to review scientific evidence of patient input
- Create patient-reported outcome (PRO) evaluation framework
- Conduct demonstrative studies adapting existing PROs
- Hold public workshop on using PROs in regulatory decisions
- Conduct PPI studies on preference sensitive conditions
- FDA Patient Preference Public Workshop – December 7-8, 2017
Conclusions

• Structural benefit-risk frameworks have proven to be important tools for systematic assessment of medical products and for communication with major stakeholders e.g., patient groups and sponsors

• Qualitative and quantitative PPI can inform medical product development (e.g., device features, clinical trial endpoint selection) and evaluation (e.g., benefit-risk assessments)

• CDRH continues to engages patients to inform regulatory decisions
18 September 2017

Ongoing Efforts to incorporate Patients’ Experiences and Perspectives into Drug Development: Patient Preferences

Brett Hauber, PhD
Senior Economist and Vice President
Health Preference Assessment
RTI Health Solutions

Affiliate Associate Professor
Graduate Program in Pharmaceutical Outcomes Research and Policy (PORPP)
University of Washington
Many organizations are interested in furthering in incorporating the patient perspective into drug and device development and evaluation:

- Regulators
- Payers
- Industry groups
- Patient groups

(to name just a few)
What Matters: An Example
What matters to patients and their families

- Rhizomelic chondrodysplasia punctate (RCDP) affects fewer than 1 in 100,000 people worldwide (ghr.nlm.nih.gov)

  - ‘…whether a drug is having an effect “can be really difficult to tease out if your working population is 10 or 20 patients,” Dr. Bober added. “It’s not like we can give this drug to 20,000 people and see what happens.”’ (http://www.nytimes.com/2015/09/07/us/flicker-of-hope-for-children-with-rare-and-devastating-disease.html)

- Quantitative patient preference methods which require large sample sizes, may not be feasible (or even necessary)

  - Simpler mixed-methods (qualitative research with quantitative outputs) may be most appropriate

*Flicker of Hope for Children With Rare and Devastating Disease - The New York Times
By ABBY GOODNOUGH SEPT. 6, 2015
What matters to patients and their families

The example of RCDP

Biologic Endpoint Approach → Increased plasmalogen levels

*Flicker of Hope for Children With Rare and Devastating Disease - The New York Times
By ABBY GOODNOUGH SEPT. 6, 2015
What matters to patients and their families

The example of RCDP

Biologic endpoint Approach  🔄  Increased plasmalogen levels

Patient-preference approach  🔄  ‘…Dr. Bober asked about the clinical trial: What kind of improvement would the parents most like to see in Jude?’

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By ABBY GOODNOUGH SEPT. 6, 2015
What matters to patients and their families

The example of RCDP

Biologic endpoint Approach → Increased plasmalogen levels

Patient-preference approach →

‘...Dr. Bober asked about the clinical trial: What kind of improvement would the parents most like to see in Jude?’

‘Stronger respiratory and immune systems, she replied. The ability to “talk to us, reach for us, hug us.”’

*Flicker of Hope for Children With Rare and Devastating Disease - The New York Times
By ABBY GOODNOUGH SEPT. 6, 2015
What matters to patients and their families

The example of RCDP

Biologic endpoint Approach → Increased plasmalogen levels

Patient-preference approach →

“One of the biggest challenges … would be figuring out ‘end points’…ways to evaluate whether the drug was providing any benefit.”

“Knowing why she’s in pain,” … “Not having to troubleshoot everything.”

“To even think he could communicate with us, or reach for things”

“…improvements… in Marley’s respiratory function and in her vision, because she is going blind”

*Flicker of Hope for Children With Rare and Devastating Disease - The New York Times By ABBY GOODNOUGH SEPT. 6, 2015*
What matters to patients and their families

The example of RCDP

Dr. Bober conducted an informal preference study to identify what matters to these parents.

"Knowing why she's in pain,"
"Not having to troubleshoot everything."
"To even think he could communicate with us, or reach for things"
"...improvements... in Marley's respiratory function and in her vision, because she is going blind"

*Flicker of Hope for Children With Rare and Devastating Disease - The New York Times By ABBY GOODNOUGH SEPT. 6, 2015*
What matters to patients and their families

The example of RCDP

Dr. Bober conducted an informal preference study to identify what matters to these parents.

Before we can measure what matters, we need to determine what matters and how much each of these things matter.

*Flicker of Hope for Children With Rare and Devastating Disease - The New York Times By ABBY GOODNOUGH SEPT. 6, 2015
Three Types of Patient Preference Information That Can Inform Benefit-Risk Assessment
## Three Types of Patient Preference Information

<table>
<thead>
<tr>
<th>Attributes</th>
<th>What Matters</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Can often be obtained using qualitative methods</td>
</tr>
<tr>
<td></td>
<td>Simple quantitative methods can be used to separate those attributes that matter to patients from those attributes that do not</td>
</tr>
</tbody>
</table>
# Three Types of Patient Preference Information

<table>
<thead>
<tr>
<th>Attributes</th>
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</tr>
<tr>
<td>Relative importance</td>
<td>How much it matters</td>
<td>Requires using quantitative methods that provide a weight for each attribute</td>
</tr>
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# Three Types of Patient Preference Information

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</tr>
</thead>
<tbody>
<tr>
<td>Relative importance</td>
<td>Can often be obtained using qualitative methods</td>
</tr>
<tr>
<td>How much it matters</td>
<td>Simple quantitative methods can be used to separate those attributes that matter to patients from those attributes that do not</td>
</tr>
<tr>
<td>Tradeoffs</td>
<td>Requires using quantitative methods that provide a weight for each attribute</td>
</tr>
<tr>
<td>How much it matters and what tradeoffs are patients willing to make</td>
<td>Patients are willing to make to obtain or avoid a given attribute.</td>
</tr>
<tr>
<td></td>
<td>Can be approximated by comparing the weights that patients assign to each attribute</td>
</tr>
<tr>
<td></td>
<td>Obtaining accurate trade-off information may require quantitative methods designed explicitly for this</td>
</tr>
</tbody>
</table>
### Three Types of Patient Preference Information

<table>
<thead>
<tr>
<th>Attributes</th>
<th>What Matters</th>
<th>Complexity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Attributes</td>
<td>Can often be obtained using qualitative methods</td>
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<td>Patients are willing to make to obtain or avoid a given attribute.</td>
<td>Obtaining accurate trade-off information may require quantitative methods designed explicitly for this</td>
</tr>
</tbody>
</table>

**Drilldown:**
- **Attributes:** What matters
- **Relative importance:** How much it matters
- **Tradeoffs:** What tradeoffs are patients willing to make
Three Approaches to Incorporating Patient Preferences in Benefit-Risk Assessment
Benefit-Risk Assessment

1. Assess benefits and harms
2. Elicit weights for benefits and harms from patient perspective
3. Apply weights to assessed benefits and harms

Source: MDICx Webinar, January 22, 2015
http://mdic.org/mdicx/#archive
Benefit-Risk Preference Assessment: Approach 1

1. Assess benefits and harms
2. Elicit weights for benefits and harms from patient perspective
3. Apply weights to assessed benefits and harms

Some preference methods are typically used as part of multi-criteria decision making

Source: MDICx Webinar, January 22, 2015
http://mdic.org/mdicx/#archive
Example: EMA Pilot Study

• “EMA conducted a pilot study to gain experience on how the collection of individual preferences can inform the regulatory review.”

• Swing weighting exercise used to weight toxicities and overall survival in myeloma and melanoma from the perspective of
  – Regulators
  – Patients and carers
  – Healthcare professionals

• Survey followed by face-to-face meetings to gather feedback and insights from participants

Postmus et al., Clinical Pharmacology & Therapeutics, 2016
Benefit-Risk Preference Assessment: Approach 2

Assess benefits and harms

Elicit weights for benefits and harms from patient perspective

Apply weights to assessed benefits and harms

Some methods focus only on eliciting weights

Source: MDICx Webinar, January 22, 2015
http://mdic.org/mdicx/#archive
Benefit-Risk Preference Assessment; Approach 2a

1. Assess benefits and harms
2. Elicit weights for benefits and harms from patient perspective
3. Apply weights to assessed benefits and harms

Some methods focus only on eliciting weights
Some methods are used to elicit one weight at a time

Source: MDICx Webinar, January 22, 2015
http://mdic.org/mdicx/#archive
Example: Parkinson’s Device Preference Study

1. Identify the outcomes important to patients, family members, and caregivers (FDA)

2. Design and conduct a patient preference assessment study (RTI (h)(s) Health Solutions)

3. Design methods for clinical trials approval based on explicit patient input (MIT)

4. Assess medical device stakeholder acceptance of clinical trial designs based on patient preference (MDIC Medical Device Innovation Consortium)

The power of the value of understanding.
Example: Parkinson’s Device Preference Study

- Preference study will elicit relative weights for each of 5 benefits and 3 risks using the threshold technique

<table>
<thead>
<tr>
<th>Benefits</th>
<th>Burdens</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increase in daily “on time” (50% decrease in “off time”)</td>
<td>Risk of (worsening) depression or anxiety</td>
</tr>
<tr>
<td>50% decrease in motor symptoms</td>
<td>Risk of serious adverse event (brain bleed)</td>
</tr>
<tr>
<td>50% decrease in PD pain</td>
<td>Increase in 1-year mortality risk</td>
</tr>
<tr>
<td>50% decrease in cognitive impairment</td>
<td></td>
</tr>
<tr>
<td>50% in medication and side effect burden</td>
<td></td>
</tr>
</tbody>
</table>
Benefit-Risk Preference Assessment: Approach 2b

1. Assess benefits and harms
2. Elicit weights for benefits and harms from patient perspective
3. Apply weights to assessed benefits and harms

Some methods focus only on eliciting weights

Some methods are used to elicit multiple weights simultaneously

Source: MDICx Webinar, January 22, 2015
http://mdic.org/mdicx/#archive
VBLOC Maestro® Rechargeable System

- First new obesity device approved by FDA since 2007
- The clinical study did not meet its original endpoint

- However, “the Agency looked at an FDA-sponsored survey relating to patient preferences of obesity devices that showed a group of patients would accept risks associated with this surgically implanted device for the amounts of weight loss expected to be provided by the device”

- The FDA-sponsored survey used a Discrete-Choice Experiment (DCE)

http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm430223.htm
Benefit-Risk Preference Assessment: Approach 3

1. Assess benefits and harms
2. Elicit weights for benefits and harms from patient perspective
3. Apply weights to assessed benefits and harms

Some methods look at actual decisions and infer weights based on differences in alternatives

Source: MDICx Webinar, January 22, 2015
http://mdic.org/mdicx/#archive
Example: Subcutaneous v. Intravenous Rituximab

• Intravenous rituximab in combination with chemotherapy can effectively treat indolent and aggressive forms of non-Hodgkin’s lymphoma.
• Subcutaneous (SC) rituximab produces non-inferior serum levels compared with intravenous (IV) rituximab.
• Genentech submitted a biologic license application (BLA) to FDA for the use of SC rituximab to treat certain blood cancers.
• Rummel et al (2017) conducted a cross-over trial with a direct preference question at the end of the trial to quantify preferences of patients for SQ and IV rituximab

Rummel et al., Annals of Oncology, 2017
## Patient Preference Methods

Many tools in the toolbox

<table>
<thead>
<tr>
<th>Group</th>
<th>Method</th>
</tr>
</thead>
<tbody>
<tr>
<td>Structured-weighting</td>
<td>• Simple direct weighting</td>
</tr>
<tr>
<td></td>
<td>• Ranking exercises</td>
</tr>
<tr>
<td></td>
<td>• Swing weighting</td>
</tr>
<tr>
<td></td>
<td>• Point allocation</td>
</tr>
<tr>
<td></td>
<td>• Analytic hierarchy process</td>
</tr>
<tr>
<td></td>
<td>• Outranking methods</td>
</tr>
<tr>
<td>Health-state utility</td>
<td>• Time tradeoff</td>
</tr>
<tr>
<td></td>
<td>• Standard gamble</td>
</tr>
<tr>
<td>Stated-preference</td>
<td>• Direct-assessment questions</td>
</tr>
<tr>
<td></td>
<td>• Threshold technique</td>
</tr>
<tr>
<td></td>
<td>• Conjoint analysis and discrete-choice experiments</td>
</tr>
<tr>
<td></td>
<td>• Best-worst scaling exercises</td>
</tr>
<tr>
<td>Revealed-preference</td>
<td>• Patient-preference trials</td>
</tr>
<tr>
<td></td>
<td>• Direct questions in clinical trials</td>
</tr>
</tbody>
</table>

- Grouping scheme meant only to facilitate discussion of methods
  - Not intended to preclude other grouping schemes
  - Some methods could be assigned to multiple groups

Key Messages

If you only remember a few things about this presentation

✓ Before we can measure how much something matters, shouldn’t we first determine what matters?
✓ Preferences can provide systematic, quantitative evidence of stakeholder perspectives on the relative weights of benefits and risks
✓ There are precedents for doing this
✓ There are multiple approaches and many tool in the toolbox for patient benefit-risk preference assessment
Patient Perspective into the FDA Benefit-Risk Framework

Presented by
Leah McCormick Howard, JD, Vice President
Government Relations and Advocacy
National Psoriasis Foundation
Our mission: to drive efforts to cure psoriatic disease and improve the lives of those affected.

- Founded in 1966 in Portland, OR
- Serve more than 2.5 million individuals annually
- The leading patient advocacy group for the more than 8 million Americans living with psoriasis and psoriatic arthritis.

As emerging research continues to demonstrate the serious, systemic effects of these chronic autoimmune diseases, our highest priority is to find a cure.

www.psoriasis.com
Challenges of Psoriatic Disease

• **8M+ Americans** or 3% of population
• **Up to 30%** w/ psoriasis develop PsA. Link to heart disease, depression & diabetes.
• **Nearly 2/3** feel angry, frustrated, helpless.
• **>50%**: psoriasis limits ability to enjoy life.
• **Nearly 30%** suffer from depression.
• **88%** of family members report same level of anxiety and depression
• **45%** moderate-severe psoriasis patients & **59%** w/ psoriatic arthritis **not** treated to the est. standards of care
• **$135B**: Economic burden of psoriasis
Incorporating the Patient Perspective

Evolving landscape

• Increasing interest, emphasis, and focus on understanding patient perspectives by industry & gov’t

• More opportunities for patients to share personal experiences, challenges, needs both inside & outside the development process
  – PFDD meetings, including externally led track
  – Open dialogues with patient communities

• More accurate patient perspectives are being discussed & considered in advisory committee hearings

• **Result** is patient community that feels more empowered to engage drug developers and regulators
Key Lessons Learned

Who

- Diversity of disease experience
- Subpopulations of community

What

- Just ask: patients have perspectives!
- Know what data you want/from whom

How

- Patient advocacy organizations have the trust of community & reach
- Engage community through many outlets – patient org, physicians, media

Why

- Patient need “why” explained to them
- What makes this interest in their perspectives different, and how will it positively impact their lives?
Greatest opportunities

- Regulators can now access more accurate, timely, and current patient perspectives in decision-making.
- Partnership opportunities with patient advocacy organizations abound:
  - Information gathering, such as risk-benefit perspective.
  - Patient preferences, real-world evidence and related information.
  - Information dissemination.
- Patient community embraces the opportunity to share perspectives particularly when doing so will make a difference.
On the flip side...challenges

- Much has occurred in the PFDD and Risk-Benefit space over the past 5 years thanks to FDASIA, 21st Century Cures, FDARA and the FDA’s actions.
- But a number of questions remain as we move to PFDD 2.0.
- For the patient community, these include:
  - Understanding fully this evolving paradigm, especially how the patient perspective will be incorporated into the risk-benefit framework.
  - Determining actions patient communities can take, both in collaboration with sponsors and independently, to capture relevant information to inform agency actions.
  - Ultimately, knowing these inputs are being considered as part of product reviews and how to be as effective as possible for our constituencies.
Realistic measures of success

- More patient perspective data is gathered (by all stakeholders) and used
- Patient perspectives are incorporated into more & more regulatory decisions
- Patient representatives have a meaningful place at the table, particularly advisory committee meetings
- Patients and patient representatives feel valued by regulators and product developers – we’re more than just a trials participant or end user
Final Thoughts & Observations

• The ball has moved quite a good distance over 5 or so years.
• Congress and the FDA as well as patients and industry appear to be committed to the tenets of patient engagement/PFDD including in the risk-benefit context.
• Patient perspective is not a substitute for solid scientific evidence. However, particularly when the call is close, scientifically rigorous patient perspective data must be considered to inform a decision.
• The era of “big data” brings with it tremendous potential for the field particularly as it will (hopefully) become easier and more cost-effective to collect relevant input.
• We applaud FDA for moving ahead on implementing key provisions, such as the guidances called for in 21st Century Cures, and hope to see additional clarity and direction to ensure the patient perspective is a key element of the risk-benefit framework.
“… There are many of us who would work with the FDA and drug companies to help them better understand what we face. We need safety and ways to obtain what we need in a drug. Our voices need to be heard and felt. We need options. There are many faces of Psoriasis and there should be many options to care for it as well that do not cost us more of our fragile health and emotions. To create and govern over something you don't have a vested interest in must be very difficult. Most of us are willing to help. We acknowledge the help that has been provided thus far but we still cry out for access and affordability along with Safety. Thank You for listening.”

– Commenter to Psoriasis PFDD public docket who has lived with psoriasis for 21 years.
FDA Public Meeting on Benefit:Risk Framework Implementation

September 18, 2017

Alicyn Campbell
*Global Head, Patient-Centered Outcomes Research for Oncology Product Development*
*Genentech, a Member of the Roche Group*
How is Efficacy “Treatment Benefit" Currently Assessed?

What does this scan tell us about how this patient feels or functions?

their symptom burden?

Figure 3: Response of Lymphadenopathy to Pazopanib –
Computed tomography scan showing (white arrows) retroperitoneal lymphadenopathy (A) at baseline and (B) after nearly complete resolution with 4 months of pazopanib treatment. The patient had a confirmed partial response by Response Evaluation Criteria in Solid Tumors (RECIST).
How is Safety “Risk” Currently Assessed?

- CTCAE Example

| Table 2 |
|-----------------|----------------|-----------------|----------------|----------------|
| Adverse events of interest occurring in ≥10% of patients. |
| AEs, n (%) | Panitumumab (n = 496) | Cetuximab (n = 503) |
| | Any grade | Grade 3/4 | Any grade | Grade 3/4 |
| Rash | 249 (50.2) | 25 (5.0) | 257 (51.1) | 18 (3.6) |
| Dermatitis acniform | 140 (28.2) | 17 (3.4) | 136 (27.0) | 14 (2.8) |
| Hypomagnesaemia | 137 (27.6) | 35 (7.0) | 91 (18.1) | 14 (2.8) |
| Diarrhoea | 92 (18.5) | 10 (2.0) | 89 (17.7) | 9 (1.8) |
| Dry skin | 83 (16.7) | 1 (0.2) | 79 (15.7) | 0 (0) |
| Pruritus | 83 (16.7) | 4 (0.8) | 89 (17.7) | 1 (0.2) |
| Fatigue | 75 (15.1) | 14 (2.8) | 89 (17.7) | 18 (3.6) |
| Decreased appetite | 70 (14.1) | 3 (0.6) | 78 (15.5) | 7 (1.4) |
| Nausea | 68 (13.7) | 4 (0.8) | 58 (11.5) | 7 (1.4) |
| Abdominal pain | 63 (12.7) | 19 (3.8) | 83 (16.5) | 14 (2.8) |
| Vomiting | 59 (11.9) | 9 (1.8) | 52 (10.3) | 7 (1.4) |
| Paronychia | 58 (11.7) | 11 (2.2) | 75 (14.9) | 9 (1.8) |
| Acne | 52 (10.5) | 3 (0.6) | 69 (13.7) | 5 (1.0) |
| Constipation | 41 (8.3) | 1 (0.2) | 74 (14.7) | 3 (0.6) |
| Pyrexia | 31 (6.3) | 2 (0.4) | 59 (11.7) | 4 (0.8) |
| Other AEs, n (%) | | | | |
| Skin toxicity | 431 (86.9) | 63 (12.7) | 440 (87.5) | 48 (9.5) |
| Infusion reactions | 14 (2.8) | 1 (0.2) | 63 (12.5) | 9 (1.8) |

# Types of Clinical Outcome Assessments to Document Benefit:Risk

<table>
<thead>
<tr>
<th>Concepts</th>
<th>Measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptoms</td>
<td>A measurement based on a report that comes from the patient (i.e., study subject) about the status of a patient's health condition without amendment or interpretation of the patient’s report by a clinician or anyone else.</td>
</tr>
<tr>
<td>Activities of daily living</td>
<td></td>
</tr>
<tr>
<td>Signs</td>
<td>A measurement based on a report that comes from a trained health-care professional after observation of a patient’s health condition. A ClinRO measure involves a clinical judgment or interpretation of the observable signs, behaviors, or other physical manifestations thought to be related to a disease or condition.</td>
</tr>
<tr>
<td>Behaviors</td>
<td></td>
</tr>
<tr>
<td>Function</td>
<td>A measurement reported by a parent, caregiver, or someone who observes the patient in daily life.</td>
</tr>
<tr>
<td>e.g., cognitive function, respiratory function</td>
<td></td>
</tr>
<tr>
<td>Test</td>
<td>A measurement based on a task(s) performed by a patient according to instructions that is administered by a health care professional. Performance outcomes require patient cooperation and motivation.</td>
</tr>
</tbody>
</table>
Current Framework: Efficacy “benefit” vs. Safety / Tolerability “risk”

- At present, benefit:risk discussed as separate and mutually exclusive concepts
  - But is this is ‘either / or’ concept?

- In oncology, the benefit (efficacy):risk (tolerability) balance shifts depending upon expectation of curability

- Need a formal framework for evaluation of evidence as part of benefit:risk

- Include overall assessment such as patient’s willingness to continue treatment?
Operationalizing Patient-Focused Drug Development

Step 1: Patient Experience Data Development
- Data Gathering
- Patient Reported Outcomes
- Quantifying Benefits/Risks

Framework for Submission to FDA

Step 2: Incorporate in FDA Guidance

Step 3: Incorporate in FDA Benefit-Risk Assessment
Is it Time for a Separate Patient Label?
Patient Relevant Evidence Examples

PRO-CTCAE Distributions at Successive Time Points

Example: Diarrhea between Arms

Arm A

Arm B

Presented at 7th Annual PRO Consortium Workshop - April 2016
Example: Patient Reported and Clinician Reported AE’s

Maximum score per item / per patient across treatment and follow-up

<table>
<thead>
<tr>
<th>Symptomatic adverse event*</th>
<th>Any level (CTCAE grade or PRO-CTCAE score ≥1), n (%)</th>
<th>High level (CTCAE grade or PRO-CTCAE score ≥3), n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Supportive care (n=46)</td>
<td>Liquid honey (n=47)</td>
</tr>
<tr>
<td><strong>Anorexia</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CTCAE</td>
<td>11 (23.9%)</td>
<td>15 (31.9%)</td>
</tr>
<tr>
<td>PRO-CTCAE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severity</td>
<td>35 (76.1%)</td>
<td>42 (89.4%)</td>
</tr>
<tr>
<td>Interference</td>
<td>25 (54.3%)</td>
<td>36 (76.6%)</td>
</tr>
<tr>
<td><strong>Anxiety</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CTCAE</td>
<td>4 (8.7%)</td>
<td>4 (8.5%)</td>
</tr>
<tr>
<td>PRO-CTCAE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frequency</td>
<td>34 (73.9%)</td>
<td>41 (87.2%)</td>
</tr>
<tr>
<td>Severity</td>
<td>33 (71.7%)</td>
<td>40 (85.1%)</td>
</tr>
<tr>
<td>Interference</td>
<td>23 (50%)</td>
<td>29 (61.7%)</td>
</tr>
<tr>
<td><strong>Cough</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CTCAE</td>
<td>14 (30.4%)</td>
<td>21 (44.7%)</td>
</tr>
<tr>
<td>PRO-CTCAE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severity</td>
<td>43 (93.5%)</td>
<td>44 (93.6%)</td>
</tr>
<tr>
<td>Interference</td>
<td>28 (60.9%)</td>
<td>34 (72.3%)</td>
</tr>
</tbody>
</table>

Abbreviations: CTCAE = Common Terminology Criteria for Adverse Events; PRO-CTCAE = Patient-Reported Outcome of the CTCAE.

* Maximum grades occurring during and after treatment are included.

† PRO-CTCAE score of 3 or 4 represents an adverse event frequency of “frequently” or “almost constantly,” severity of “severe” or “very severe,” or interference with usual or daily activities of “quite a bit” or “very much.”
Example: Preference & Reasons for Preferring Rituxan SC Administration

- Patients were asked to give TWO reasons for their preference, if any
- Options for “Reasons for Preference” were based on the experience from PrefHer, where the reasons were captured by free text,
- The choices given for PrefMab were the 4 most commonly given reasons in PrefHer, and "Other: specify".
Is it Time for a Patient Label?

- Systematic inclusion of the patient voice in clinical trials creates large amounts of data that frequently requires descriptive analysis and presentation at the item / concept level.

- Expectation that this data is accessible to patients via PRO manuscripts does not consider the cost to obtain manuscripts, and the analysis methods (e.g. hazard ratios) are not accessible to patients.
Policy Trends in Action

- **21st Century Cures:**
  - New ‘patient experience” section / statement in label
  - Includes assessment of patient preference in regulatory decision making
    - Included in March 29, 2017 Rituxan SC ODAC & Hycela label

“Sec 3001, patient experience data:

“data that are (1) collected by any persons, including patients, family members, and caregivers of patients, patient advocacy organizations, disease research foundations, researchers and drug manufacturers and (2) are intended to provide info about patients experiences with a disease or condition including“

(A) impact of such a disease or condition or related therapy on patient’s lives,
(B) patient preferences with respect to treatment of such disease or condition
Summary

- PFDD was successful at demonstrating the value of the patient perspective in drug development.

- It is important for future frameworks to recognize the assessment of benefit:risk needs to be done in tandem and requires systematic patient input.

- A more specific evaluatory framework is essential for sponsors to generate the evidence FDA requires for this analysis.

- As we look forward, leveraging synergies with the upcoming PDUFA VI patient centricity guidances, as well as expanded use of patient preference methods will be key for success.
Session 2
Panel Discussion and Q&A

Pujita Vaidya
Facilitator

September 18, 2017
BREAK
Session 3
Special Topics in Benefit-Risk Assessment

Sara Eggers
Facilitator

September 18, 2017
Asking Questions People Can Answer

Baruch Fischhoff
Department of Engineering and Public Policy
Institute for Politics and Strategy
Carnegie Mellon University
http://www.cmu.edu/epp/people/faculty/baruch-fischhoff.html

Food and Drug Administration
Public Meeting on Benefit-Risk Framework Implementation

September 18, 2017
Implementation Requires Judgments

Beliefs
Experts: meaning and quality of evidence
Non-experts: perceived benefits and risks

Values
Priorities
Tradeoffs
Judgments Fill the Cells of the Benefit-Risk Framework

Figure 1: FDA Benefit-Risk Framework

<table>
<thead>
<tr>
<th>Decision Factor</th>
<th>Evidence and Uncertainties</th>
<th>Conclusions and Reasons</th>
</tr>
</thead>
<tbody>
<tr>
<td>Analysis of Condition</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current TreatmentOptions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Benefit</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Risk</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Risk Management</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Benefit-Risk Summary Assessment</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Criteria for Evaluating Judgments

Reliability
- Inter-temporal
- Inter-judge
- Inter-method

Validity
- Face (social acceptable)
- Coherence (internal consistency)
- Construct (theoretically posited correlations)
Unsound Judgments Might

Obscure value-laden assumptions
Frustrate orderly responses
Misrepresent respondents
Obscure Value-Laden Assumptions

Handling Protest Responses in Contingent Valuation Surveys

Mark Pennington, PhD, Manuel Gomes, PhD, Cam Donaldson, PhD

There are well-documented challenges to the implementation of CV, including strategic responses, anchoring or framing effects, and refusal to engage with a request to state a WTP value or accept/reject a given value (protesting). This paper focuses on the specific issue of protesting. Respondents commonly refuse to state a WTP value or indicate their acceptance/rejection of a given value in CV surveys. This may be because they place zero value on the commodity. Alternatively, respondents may object to the principle of placing a monetary value on the commodity, or they may feel strongly that the responsibility for provision falls on another actor, such as the Government. Differentiating between

Obscure Value-Laden Assumptions

Determinants of protest responses in environmental valuation: A meta-study
Jürgen Meyerhoff \textsuperscript{a,*,} Ulf Liebe \textsuperscript{b,c}

Table 1
Predictors of protesting used in the analysis.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Description</th>
<th>Mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>\textit{Elicitation format (EF)}</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CE</td>
<td>1 if choice experiment is used in sample</td>
<td>0.13</td>
</tr>
<tr>
<td>DC</td>
<td>1 if dichotomous choice format (comprising SBDC, DBDC, HBDC, and IB [iterative bidding]) is used in sample</td>
<td>0.43</td>
</tr>
<tr>
<td>OE</td>
<td>1 if open ended question format is used in sample</td>
<td>0.19</td>
</tr>
<tr>
<td>PC</td>
<td>1 if payment card is used in sample</td>
<td>0.24</td>
</tr>
<tr>
<td>EF_other</td>
<td>1 if question format is other than CE, DC, OE, or PC</td>
<td>0.02</td>
</tr>
<tr>
<td>\textit{Payment vehicle (PV)}</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TAX</td>
<td>1 if tax is payment vehicle</td>
<td>0.36</td>
</tr>
<tr>
<td>DONA</td>
<td>1 if donation is payment vehicle</td>
<td>0.09</td>
</tr>
<tr>
<td>BILL</td>
<td>1 if a surcharge to a bill (e.g., water bill) is payment vehicle</td>
<td>0.20</td>
</tr>
<tr>
<td>FUND</td>
<td>1 if fund is payment vehicle</td>
<td>0.13</td>
</tr>
<tr>
<td>ENTRA</td>
<td>1 if entrance fee is payment vehicle</td>
<td>0.09</td>
</tr>
</tbody>
</table>

Obscure Value-Laden Assumptions

An Approach to Reconciling Competing Ethical Principles in Aggregating Heterogeneous Health Preferences

Barry Dewitt, MSc, Alexander Davis, PhD, Baruch Fischhoff, PhD, Janel Hanmer, MD, PhD

Background. Health-related quality of life (HRQL) scores are used extensively to quantify the effectiveness of medical interventions. Societal preference-based HRQL scores aim to produce societal valuations of health by aggregating valuations from individuals in the general population, where each aggregation procedure embodies different ethical principles, as explained in social choice theory. Methods. Using the Health Utilities Index as an exemplar, we evaluate societal preference-based HRQL measures in the social choice theory framework. Results. We find that current preference aggregation procedures are typically justified in terms of social choice theory. However, by convention, they use only one of many possible aggregation procedures (the mean). Central to the choice of aggregation procedure is how to treat preference heterogeneity, which can affect analyses that rely on HRQL scores, such as cost-effectiveness analyses. We propose an analytical-deliberative framework for choosing one (or a set of) aggregation procedure(s) in a socially credible way, which we believe to be analytically sound and empirically tractable, but leave open the institutional mechanism needed to implement it. Conclusions. Socially acceptable decisions about aggregating heterogeneous preferences require eliciting stakeholders’ preferences among the set of analytically sound procedures, representing different ethical principles. We describe a framework for eliciting such preferences for the creation of HRQL scores, informed by social choice theory and behavioral decision research. Key words: health state preferences; health-related quality of life; health utility; equity; cost-effectiveness analysis. (Med Decis Making XXXX;XX:xx–xx)
Obscure Value-Laden Assumptions

The realities of risk-cost-benefit analysis

Baruch Fischhoff

http://dx.doi.org/10.1126/science.aaa6516
Frustrate Orderly Responses

Exclusion Criteria in National Health State Valuation Studies: A Systematic Review

Lidia Engel, MSc, Nick Bansback, PhD, Stirling Bryan, PhD, Mary M. Doyle-Waters, MLIS, David G. T. Whitehurst, PhD

Background. Health state valuation data are often excluded from studies that aim to provide a nationally representative set of values for preference-based health-related quality of life (HRQoL) instruments. The purpose was to provide a systematic examination of exclusion criteria used in the derivation of societal scoring algorithms for preference-based HRQoL instruments. Methods. Data sources included MEDLINE, official instrument websites, and publication reference lists. Analyses that used data from national valuation studies and reported a scoring algorithm for a generic preference-based HRQoL instrument were included. Data extraction included exclusion criteria and associated justifications, exclusion rates, the characteristics of excluded respondents, and analyses that explored consequential implications of exclusion criteria on the respective national tariff. Results. Seventy-six analyses (from 70 papers) met the inclusion criteria. In addition to being excluded for logical inconsistencies, respondents were often excluded if they gave the same value to all health states. Numerous other exclusion criteria were identified, with varying degrees of justification, often based on an assumption that respondents did not understand the task or as a consequence of the chosen statistical modeling techniques. Rates of exclusion ranged from 0% to 65%, with excluded respondents more likely to be older, less educated, and less healthy. Limitations included that the database search was confined to MEDLINE; study selection focused on national valuation studies that used standard gamble, time tradeoff, and/or visual analog scale techniques; and only English-language studies were included. Conclusion. Exclusion criteria used in national valuation studies vary considerably. Further consideration is necessary in this important and influential area of research, from the design stage to the reporting of results. Key words: exclusion criteria; health state valuation; preference-based measures; quality-adjusted life year. (Med Decis Making 2016;36:798-810)
Frustrate Orderly Responses

Exclusion Criteria

All states valued the same
Fewer than $x$ health states valued
More than $x$ logical inconsistencies
Incomplete/missing data
Dead $> \text{all/several states}$
Dead $\geq \text{EQ-5D full health}$
Death and/or EQ-5D full health not valued
“Pits” state not valued
Extreme values
Other
No exclusion criteria (either none reported or none applied)
Figure 2  Proportion of excluded respondents, by valuation technique, with different markers used to indicate different preference-based health-related quality of life instruments (n = 55). The proportion of excluded respondents was reported in 55 (72%) studies, ranging from 0% to 65%. No exclusion rates were reported in studies for the QWB-SA. Exclusion rates relate to excluded respondents (not the exclusion of individual valuations). AQoL = Assessment of Quality of Life; HUI = Health Utilities Index; QWB-SA = Quality of Well-Being Self-Administered Scale; SG = standard gamble; TTO = time tradeoff; VAS = visual analog scale.
Misrepresent Respondents

Figure 2
Estimates of Fertility Expectations of American Women: Proportion of Women Expecting No Further Children in (a) All Future Years, and (b) the Next Five Years.

Misrepresent Respondents

13. Judgements of the probability of dying in the next year, from a large representative sample of American teens

To Ask Questions People Can Answer

Consult the elicitation literature broadly. Involve respondents in development. Evaluate critically; report candidly.
Consult Literature Broadly (Beliefs)

Use (and abuse) of expert elicitation in support of decision making for public policy

M. Granger Morgan
Department of Engineering and Public Policy, Carnegie Mellon University, Pittsburgh, PA 15213

Edited by William C. Clark, Harvard University, Cambridge, MA, and approved March 18, 2014 (received for review October 22, 2013)

The elicitation of scientific and technical judgments from experts, in the form of subjective probability distributions, can be a valuable addition to other forms of evidence in support of public policy decision making. This paper explores when it is sensible to perform such elicitation and how that can best be done. A number of key issues are discussed, including topics on which there are, and are not, experts who have knowledge that provides a basis for making informed predictive judgments; the inadequacy of only using qualitative uncertainty language; the role of cognitive heuristics and of overconfidence; the choice of experts; the development, refinement, and iterative testing of elicitation protocols that are designed to help experts to consider systematically all relevant knowledge when they make their judgments; the treatment of uncertainty about model functional form; diversity of expert opinion; and when it does or does not make sense to combine judgments from different experts. Although it may be tempting to view expert elicitation as a low-cost, low-effort alternative to conducting serious research and analysis, it is neither. Rather, expert elicitation should build on and use the best available research and analysis and be undertaken only when, given those, the state of knowledge will remain insufficient to support timely informed assessment and decision making.

Consult Literature Broadly (Values)

Chapter 18

COGNITIVE PROCESSES IN STATED PREFERENCE METHODS

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Involve Respondents in Development

The Voice of the Patient

A series of reports from the U.S. Food and Drug Administration’s (FDA’s) Patient-Focused Drug Development Initiative

Chronic Fatigue Syndrome and Myalgic Encephalomyelitis

Public Meeting: April 25, 2013
Report Date: September 2013
Involve Respondents in Development

![Diagram of FDA Benefit-Risk Framework]

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

<table>
<thead>
<tr>
<th>Decision Factor</th>
<th>Evidence and Uncertainties</th>
<th>Conclusions and Reasons</th>
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<td>Analysis of Condition</td>
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<td>Current Treatment Options</td>
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<td>Risk</td>
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<td>Risk Management</td>
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**Benefit-Risk Summary Assessment**

Decision Science Principles in FDA’s Benefit-Risk Framework

Recognizes scientific and policy judgment in all analyses
Quantifies the quantifiable, without ignoring other concerns
Highlights ethical and political tradeoffs, rather than burying them in a metric
Supports risk management

TABLE 6-4 Example of an Adapted Benefit-Risk Framework for Approval of Opioid Products

<table>
<thead>
<tr>
<th>Decision Factor</th>
<th>Evidence and Uncertainties</th>
<th>Conclusions and Reasons</th>
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<tr>
<td>Characteristics of Opioid</td>
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<td>Benefits Observed in Clinical Trials, Overall</td>
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<td>• Benefits to patients</td>
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<td>• Public health risks</td>
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<td>Predicted Benefits/Risks to Families of Patients</td>
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<td>Predicted Benefits/Risks to Society, Overall</td>
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<td>• Special communities</td>
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<td>• Subpopulations</td>
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<td>Diversion Potential</td>
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<td>Predicted Effects on Use of Other Opioids or Illicit Drugs</td>
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<td>Risk Management, Overall</td>
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<tr>
<td>• Potential for off-label use</td>
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<td>• Advertising/promotion</td>
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Evaluate Critically; Report Candidly

Reliability
Inter-temporal
Inter-judge
Inter-method

Validity
Face (social acceptable)
Coherence (internal consistency)
Construct (theoretically posited correlations)
Evaluate Critically; Report Candidly

Public Understanding of Ebola Risks: Mastering an Unfamiliar Threat

Baruch Fischhoff,¹ Gabrielle Wong-Parodi,¹,* Dana Rose Garfin,² E. Alison Holman,³ and Roxane Cohen Silver²,⁴

R₀: If someone gets Ebola in the US, how many people do you think will catch it from them directly?

Evaluate Critically; Report Candidly

Public Understanding of Ebola Risks: Mastering an Unfamiliar Threat
Baruch Fischhoff,1 Gabrielle Wong-Parodi,1,* Dana Rose Garfin,2 E. Alison Holman,3 and Roxane Cohen Silver2,4

R₀: If someone gets Ebola in the US, how many people do you think will catch it from them directly?

Fig. 1. Judgments of R₀ (pooling values used by <1% of respondents).

A Frontier: Uncertainty

Characterizing and Communicating Uncertainty in the Assessment of Benefits and Risks of Pharmaceutical Products

Workshop Summary

http://www.nap.edu/catalog.php?record_id=18870
A Frontier: Uncertainty

Confidence intervals: Variability in observations
Internal validity (how good were studies) External validity (how well do studies generalize) Pedigree (how good is underlying science) Credible intervals: Summary of uncertainties

Potential Areas for Quantitative Benefit-Risk Assessments

Richard A. Forshee, PhD
Center for Biologics Evaluation and Research
Office of Biostatistics and Epidemiology

September 18, 2017
FDA Must Consider Many Types of Data From Many Sources

Data for Decisions

Contributions by Scientific Community and Industry
- Industry
  - Basic data
- Scientific Literature
  - Data
- Universities
  - Data, Consultation
- National Research Council
  - Data, Consultation, Special problems
- Hospitals, Clinics & Private Physicians
  - Data, Drug experience
- Outside Experts
  - Special problems

Contributions by FDA and Government
- FDA Office of Commissioner
  - Coordination and review, Issuance of regulations
- FDA Bureau of Biological and Physical Sciences
  - Scientific evaluation, Testing
- FDA Bureau of Medicine
  - Medical evaluations, Monitoring of NDA's
- FDA District Office Laboratories
  - Checks industry data, Checks industry facilities and controls, Testing
- U.S. Department of Agriculture
  - Certifies usefulness of pesticides, Data, Consultation
- Public Health Service
  - Data, Consultation
- National Science Foundation
  - Data, Consultation
- Department of Interior & Other Gov't.
  - Data, Consultation

Approval or Disapproval

https://www.flickr.com/photos/fdaphotos/8205558579/in/album-72157624615595535/
“During Senate testimony in 1964, Commissioner George Larrick used this chart to illustrate the length to which, ‘in deciding whether to approve or disapprove a given proposal, FDA reaches beyond its own staff to obtain data and advice.’”
Complex System for Managing the Risks of Medical Products

From Managing the Risks From Medical Product Use, FDA Report, 1999
Benefit-Risk Assessment is a complex, iterative process involving many participants. Qualitative approaches are usually sufficient, but quantitative approaches can improve the quality of the decision-making process in some cases.
FDA/CBER Has Built Capacity for Quantitative BRA

- Analytics and Benefit-Risk Assessment (ABRA) team in CBER/OBE
- Several quantitative benefit-risk assessments have been presented at Advisory Committees and published
- Engaged in internal and external training
Advancing risk assessment for emerging infectious diseases for blood and blood products: proceedings of a public workshop

Lou M. Gallagher, Peter R. Ganz, Hong Yang, Debra A. Kessler, Sheila F. O'Brien, Brian S. Custer, Michael P. Busch, Roger Y. Dodd, Susan L. Stramer, Mark O. Walderhaug, Richard A. Forshee, Alan E. Williams, Jay S. Epstein, and Steven A. Anderson

Overview of Benefit–Risk Evaluation Methods: A Spectrum from Qualitative to Quantitative

George Quartey, Chunlei Ke, Christy Chuang-Stein, Weili He, Qi Jiang, Kao-Tai Tsai, Guochen Song, and John Scott
ICH Benefit-Risk Guidelines

Key idea: “provide a succinct, integrated, and clearly explained benefit risk assessment of the medicinal product for its intended use”

ICH BR Expert Working Group
Lisbon, Portugal 2016
Applicants May Submit Quantitative BRA

“A descriptive approach that explicitly communicates the interpretation of the data and the benefit-risk assessment will generally be adequate.”

“An applicant may choose to use methods that quantitatively express the underlying judgments and uncertainties in the assessment. Analyses that compare and/or weigh benefits and risks using the submitted evidence may be presented.”

Emphasis Added
ICH M4E(R2),
http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/CTD/M4E_R2_Efficacy/M4E_R2__Step_4.pdf
Things to Consider
Modeling Uncertainty and Variability

• All inputs in a model may have some uncertainty or variability.
  – Uncertainty can theoretically be reduced with additional data
  – Variability is an inherent property

• Models must accurately convey uncertainty and variability

• Simulations and probability distributions are commonly used to represent uncertainty and variability
Sensitivity Analysis and Validation

• Benefit-Risk assessments should include sensitivity analysis
  – Which inputs have the most impact on the model results?
  – Which model assumptions are most critical?
  – What additional research could improve the model?

• When possible, models should be validated against external data sets that were not used to construct the model
Concluding Thoughts
Value of Benefit-Risk Assessment

• Provides a framework for discussion

• Assists in the integration of large amounts of data

• Identifies uncertainty and data gaps
Value of Benefit-Risk assessment

• Facilitates the comparison of possible policy alternatives

• Improves transparency and risk communication
  – Caveat: Complexity of risk assessment models can appear to be “black boxes” if they aren’t communicated well
Limitations of Benefit-Risk Assessment

• Garbage In, Garbage Out
• Risk assessment models are only as good as the scientific theory and data on which they are built
• If uncertainty is high, the best decision may not be clear
• Changing circumstances or new scientific discoveries may force significant updates to a risk assessment
Benefit-Risk Assessment Does Not Replace Risk Management

• Judgment is still required to choose the most appropriate option
  – Clinical
  – Regulatory Policy
  – Legal Considerations
Thank you!
Communicating Benefit-Risk to the Public

Steven Woloshin, MD, MS & Lisa M. Schwartz, MD, MS

Center for Medicine and the Media,
The Dartmouth Institute for Health Policy and Clinical Practice, Dartmouth Medical School
Confusion about the meaning of FDA approval

Nearly half of U.S. adults mistakenly believed FDA only approves—and only permits advertising of—extremely effective drugs or drugs without serious side effects.

Schwartz, Woloshin, JAMA Int Med 2011

Most U.S. physicians mistakenly believed approval means the drug is as effective as others for this condition.

Kesselheim, Woloshin, Schwartz, JAMA, 2016

Drug approval means FDA believes benefit outweighs harm - NOT that benefits are important or drug is very safe.
FDA Benefit-Risk Assessment helps

Allows prescribers and consumers to understand the real meaning of approval.

Provides FDA’s rationale for approving a new drug and how they weighed benefit and risk.

Unique source of independent analysis and interpretation – not filtered or negotiated with industry – otherwise hard to find.
Newly approved drug

SILIQ™ (brodalumab) injection 210 mg/1.5 mL

NOW APPROVED AND AVAILABLE

Prescribing Information
Medication Guide
Instructions for Use
About SILIQ REMS
Visit VALEANT.com
Brodalumab — Brodalumab, an anti-IL-17 receptor A monoclonal antibody, has demonstrated high efficacy for psoriasis. In February 2017, the FDA approved brodalumab for the treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy and have failed to respond or have lost response to other systemic therapies [174]. In the United States, use of the drug will require participation in a Risk Evaluation and Mitigation Strategy program due to concerns regarding risk for suicidal ideation and completed suicides in treated patients.

Data from phase III randomized trials support the efficacy of brodalumab for moderate to severe plaque psoriasis [175,176]. In two identically designed trials (AMAGINE-2 [n = 1831] and AMAGINE-3 [n = 1881]), patients were assigned in a 2:2:1:1 ratio to receive brodalumab 210 mg every two weeks; brodalumab 140 mg every two weeks; standard dosing of ustekinumab on day 1, week 4, and then every 12 weeks (45 mg dose if body weight ≤100 kg, 90 mg dose if body weight >100 kg); or placebo. At week 12, more patients receiving 210 mg of brodalumab or 140 mg of brodalumab achieved PASI 75 compared with patients in the placebo group (86, 67, and 8 percent, respectively [AMAGINE-2], and 85, 69, and 6 percent, respectively [AMAGINE-3]). In addition, the rate of complete clearance of skin disease (PASI 100) at week 12 was higher among patients given 210 mg of brodalumab compared with patients receiving ustekinumab (44 versus 22 percent, respectively [AMAGINE-2], and 37 versus 19 percent, respectively [AMAGINE-3]). A statistically significant benefit of the 140 mg dose of brodalumab over ustekinumab for achieving PASI 100 was evident in AMAGINE-3 at week 12 but not in AMAGINE-2. Mild to moderate Candida infections were more frequent in the brodalumab groups than in the ustekinumab and placebo groups, and neutropenia occurred more frequently in the brodalumab and ustekinumab groups than in the placebo group. In addition, two suicides occurred in patients receiving brodalumab in crossover and open-label phases of AMAGINE-2.
**Brodalumab** — Brodalumab, an anti-IL-17 receptor A monoclonal antibody, has demonstrated high efficacy for psoriasis. In February 2017, the FDA approved brodalumab for the treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy and have failed to respond or have lost response to other systemic therapies [174]. In the United States, use of the drug will require participation in a Risk Evaluation and Mitigation Strategy program due to concerns regarding risk for suicidal ideation and completed suicides in treated patients.

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Phase 3 Studies Comparing Brodalumab with Ustekinumab in Psoriasis

RESULTS
At week 12, the PASI 75 response rates were higher with brodalumab at the 210-mg and 140-mg doses than with placebo (86% and 67%, respectively, vs. 8% [AMAGINE-2] and 85% and 69%, respectively, vs. 6% [AMAGINE-3]; P<0.001); the rates of sPGA scores of 0 or 1 were also higher with brodalumab (P<0.001). The week 12 PASI 100 response rates were significantly higher with 210 mg of brodalumab than with ustekinumab (44% vs. 22% [AMAGINE-2] and 37% vs. 19% [AMAGINE-3], P<0.001). The PASI 100 response rates with 140 mg of brodalumab were 26% in AMAGINE-2 (P = 0.08 for the comparison with ustekinumab) and 27% in AMAGINE-3 (P = 0.007). Rates of neutropenia were higher with brodalumab and with ustekinumab than with placebo. Mild or moderate candida infections were more frequent with brodalumab than with ustekinumab or placebo. Through week 52, the rates of serious infectious episodes were 1.0 (AMAGINE-2) and 1.3 (AMAGINE-3) per 100 patient-years of exposure to brodalumab.
CONCLUSION

[Siliq] resulted in significant clinical improvements in patients with moderate-to-severe psoriasis.

ABSTRACT

Early clinical studies suggested that the anti-interleukin-17 receptor A monoclonal antibody brodalumab has efficacy in the treatment of psoriasis.

METHODS

In two phase 3 studies (AMAGINE-2 and AMAGINE-3), patients with moderate-to-severe psoriasis were randomly assigned to receive brodalumab (210 mg or 140 mg every 2 weeks), ustekinumab (45 mg for patients with a body weight ≤100 kg and 90 mg for patients >100 kg), or placebo. At week 12, patients receiving brodalumab were randomly assigned again to receive a brodalumab maintenance dose of 210 mg every 2 weeks or 140 mg every 2 weeks, every 4 weeks, or every 8 weeks; patients receiving ustekinumab continued to receive ustekinumab every 12 weeks.
Suicide only briefly mentioned in results.
FDA Office Director Benefit-Risk Summary

Benefit-Risk Summary and Assessment
Siliq (brodalumab) is a subcutaneously administered human interleukin-17 receptor A antagonist. This memo documents my rationale for my Approval recommendation for BLA 761032 for Siliq (brodalumab) injection for the treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy and have failed to respond or have lost response to other systemic therapies.

The efficacy of Siliq was established in three pivotal phase 3 trials. Relative to placebo, Siliq 210 mg every 2 weeks demonstrated superiority on the co-primary endpoints of proportion of subjects with sPGA of 0 or 1 at Week 12 and proportion of subjects with PASI 75 at Week 12, as well as the key secondary endpoints of PASI 100, and sPGA of 0 at Week 12. Across the phase 3 trials, response rates for PASI 75 ranged from 83% to 86% in patients treated with Siliq, versus 3% to 8% in the placebo group; response rates for sPGA of 0 or 1 ranged from 76% to 80% in patients treated with Siliq, versus 1% to 4% in the placebo group. The maximal effect of Siliq on sPGA of 0 or 1 was achieved by week 12, with some gain in responders with treatment from week 12 to week 16, but limited probability of becoming a responder beyond week 16.

The efficacy of Siliq (brodalumab) is not in dispute. Siliq is a highly efficacious treatment, but when viewed in the context of already approved psoriasis therapies, the additional benefits appear nominal. In cross-trial comparisons, Siliq's efficacy on PASI 75 and sPGA 0 or 1 is comparable to that of infliximab and ixekizumab, and efficacy on PASI 100 is similar between Siliq and ixekizumab. Its subcutaneous route of administration is preferable to the intravenous administration required for infliximab, but is shared by all of the other approved biologics for psoriasis. Its maintenance dosing regimen places it among the least favorable of the approved biologics: ustekinumab requires dosing every 12 weeks; infliximab every 8 weeks; secukinumab and ixekizumab every 4 weeks; while Siliq and adalimumab require dosing every 2 weeks. An important benefit of Siliq may be its efficacy in patients who have failed prior biologic therapies. In post-hoc analyses of PASI-75 response in
“The efficacy of Siliq (brodalumab) is not in dispute….”

“However, the presence of a rare, fatal event observed in a controlled clinical trial setting is merely the ‘tip of the iceberg’. Once approved and used in a broader population, we can anticipate a higher occurrence.”

“Further, I am unaware of any product having been approved by the FDA with four completed suicides in a clinical development program.”
FDA’s reasoning has great clinical value

“I have considered … the seriousness of the disease, the chronic nature of the disease, the variability in response and duration of response to different treatments, patient’s ability to access various approved treatments, the impact of the disease on patients and their families, and the continued unmet medical need…..”

“Perhaps most importantly, I have considered the importance of patient autonomy. I believe that patients should have choice, but that choice must be informed.”
FDA’s reasoning has great clinical value

Office Director’s thoughtful summary explains how FDA balanced benefits and risks.

Drug was approved with risk mitigation strategies including:

- Boxed warning
- Limit use to patients who failed other systemic therapy
- REMS
Suggestions for FDA:
Communication of Benefit-Risk Summary and Assessment

1. Organize narrative with visually distinct, named sections
Benefit-Risk Summary and Assessment

Siliq (brodalumab) is a subcutaneously administered human interleukin-17 receptor A antagonist. This memo documents my rationale for my Approval recommendation for BLA 761032 for Siliq (brodalumab) injection for the treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy and have failed to respond or have lost response to other systemic therapies. The efficacy of Siliq was established in three pivotal phase 3 trials. Relative to placebo, Siliq 210 mg every 2 weeks demonstrated superiority on the co-primary endpoints of proportion of subjects with sPGA of 0 or 1 at Week 12 and proportion of subjects with PASI 75 at Week 12, as well as the key secondary endpoints of PASI 100, and sPGA of 0 at Week 12. Across the phase 3 trials, response rates for PASI 75 ranged from 83% to 86% in patients treated with Siliq, versus 3% to 8% in the placebo group; response rates for sPGA of 0 or 1 ranged from 76% to 80% in patients treated with Siliq, versus 1% to 4% in the placebo group. The maximal effect of Siliq on sPGA of 0 or 1 was achieved by week 12, with some gain in responders with treatment from week 12 to week 16, but limited probability of becoming a responder beyond week 16. The efficacy of Siliq (brodalumab) is not in dispute. Siliq is a highly efficacious treatment, but when viewed in the context of already approved psoriasis therapies, the additional benefits appear nominal. In cross-trial comparisons, Siliq's efficacy on PASI 75 and sPGA 0 or 1 is comparable to that of infliximab and ixekizumab, and efficacy on PASI 100 is similar between Siliq and ixekizumab. Its subcutaneous route of administration is preferable to the intravenous administration required for infliximab, but is shared by all of the other approved biologics for psoriasis. Its maintenance dosing regimen places it among the least favorable of the approved biologics: ustekinumab requires dosing every 12 weeks; infliximab every 8 weeks; secukinumab and ixekizumab every 4 weeks; while Siliq and adalimumab require dosing every 2 weeks. An important benefit of Siliq may be its efficacy in patients who have failed prior biologic therapies. In post-hoc analyses of PASI-75 response in patients who had failed previous biologic psoriasis therapies, 82% of Siliq-treated patients achieved success across the three phase 3 trials, and PASI-90 and PASI-100 response rates were 65% and 35%, respectively. These patients, with more limited treatment options, may be willing to tolerate a greater level of risk to achieve benefit.
Benefit-Risk Summary and Assessment

Siliq (brodalumab) is a subcutaneously administered human interleukin-17 receptor A antagonist.

Indication: This medication is indicated for patients who are candidates for systemic therapies

Benefit: The efficacy of Siliq 210 mg every 2 weeks for Week 12 to Week 24 was 86% in PASI 100, and sPGA of 0 or 1 at Week 12 and Week 24, respectively. The maximal effect of Siliq on PASI 100 was observed at Week 12 (brodalumab) is not available for prior biologic therapies, psoriasis therapies 90 and PASI-100 results for patients, may be worth considering.

Comparative efficacy: In cross-trial comparisons, Siliq’s efficacy on PASI 75 and sPGA 0 or 1 is comparable to that of infliximab and ixekizumab, and efficacy on PASI 100 is similar between Siliq and ixekizumab. Its subcutaneous route of administration is preferable to the intravenous administration required for infliximab, but is shared by all of the other approved biologics for psoriasis. Its maintenance dosing regimen places it among the least favorable of the approved biologics: ustekinumab

Possible headers:

- Indication
- Benefit
- Risk
- Comparative efficacy
- Weighing benefit and risk
- Risk management
- Post-market requirements
Suggestions for FDA:
Communication of Benefit-Risk Summary and Assessment

1. Organize narrative with visually distinct, named sections

2. Include structured tables with trial descriptions and efficacy and side effect data
   - Basis of drug approval
Benefit-Risk Summary and Assessment

Siliq (brodalumab) is a subcutaneously administered human interleukin-17 receptor A antagonist. This memo:

- Benefit appears over 6 pages
- Risks over 7 pages

Sometimes quantified, sometimes just “p-values”

Structured tables (and consistent data formats) make it easier for readers:
- Avoids long text bogged down with lots of numbers
- Text can focus on interpretation

While Siliq shares safety concerns with other approved biologic psoriasis therapies (Crohn’s disease exacerbation, infections, TB reactivation, response to live vaccines), the serious risk unique to Siliq is completed suicide. Four completed suicides (0.09%) occurred in subjects treated with SILIQ in the psoriasis pm, compared with none in placebo subjects. Across all clinical development pms for SILIQ, there were 6 completed suicides. The applicant has argued that the completed suicides represent the background risk in the
# Benefit

**Who was in the trials?**  
Adults (69% men); ages 18 to 75 (average 45)  
Stable moderate to severe plaque psoriasis for ≥ 6 months

<table>
<thead>
<tr>
<th></th>
<th>Trial 3</th>
<th>Trial 4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Design</strong></td>
<td>Double-blind, superiority</td>
<td>Double-blind, superiority</td>
</tr>
<tr>
<td><strong>Duration</strong></td>
<td>12 weeks</td>
<td>12 weeks</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th><strong>Siliq</strong></th>
<th><strong>Stelara</strong></th>
<th><strong>Placebo</strong></th>
<th><strong>Siliq</strong></th>
<th><strong>Stelara</strong></th>
<th><strong>Placebo</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Psoriasis better?</strong></td>
<td>n=612</td>
<td>n=300</td>
<td>n=309</td>
<td>n=624</td>
<td>n=313</td>
<td>n=311</td>
</tr>
<tr>
<td><strong>Primary outcomes</strong></td>
<td>210mg SQ</td>
<td>45mg SQ</td>
<td>No drug SQ</td>
<td>210mg SQ</td>
<td>45mg SQ</td>
<td>No drug SQ</td>
</tr>
<tr>
<td><strong>every 2 weeks</strong></td>
<td>every 2 weeks 4</td>
<td>week 0 and every 2 weeks</td>
<td>every 2 weeks 4</td>
<td>week 0 and every 2 weeks</td>
<td>week 0 and every 2 weeks</td>
<td></td>
</tr>
<tr>
<td><strong>Major improvement</strong></td>
<td>≥ 75% improved psoriasis score - PASI 75</td>
<td></td>
<td></td>
<td>≥ 75% improved psoriasis score - PASI 75</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>83%</td>
<td>70%</td>
<td>8%</td>
<td>85%</td>
<td>69%</td>
<td>6%</td>
</tr>
<tr>
<td><strong>Minimal or no psoriasis</strong></td>
<td>Physician rated skin clear almost clear - sPGA= 0/1</td>
<td></td>
<td></td>
<td>Physician rated skin clear almost clear - sPGA= 0/1</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>79%</td>
<td>61%</td>
<td>4%</td>
<td>80%</td>
<td>57%</td>
<td>4%</td>
</tr>
<tr>
<td><strong>Secondary outcomes</strong></td>
<td>No psoriasis</td>
<td></td>
<td></td>
<td>No psoriasis</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Physician rated skin clear - sPGA= 0</strong></td>
<td>45%</td>
<td>21%</td>
<td>1%</td>
<td>37%</td>
<td>19%</td>
<td>&lt;1%</td>
</tr>
</tbody>
</table>
### Benefit

**Who was in the trials?** Adults (69% men); ages 18 to 75 (average 45)
Stable moderate to severe plaque psoriasis for $\geq 6$ months

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<td>210mg SQ every 2 weeks</td>
<td>45mg SQ week 0 and 4 weeks</td>
<td>No drug SQ every 2 weeks</td>
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<td></td>
<td></td>
</tr>
<tr>
<td><strong>Minimal or no psoriasis</strong></td>
<td>almost clear, sPGA=0/1</td>
<td>Physician rated skin clear</td>
<td></td>
</tr>
<tr>
<td><strong>Secondary outcomes</strong></td>
<td>no psoriasis</td>
<td>Physician rated skin clear - sPGA= 0</td>
<td></td>
</tr>
</tbody>
</table>
## Side effects

### Black Box Warning

**Suicidal thoughts and behaviors including completed suicides**

<table>
<thead>
<tr>
<th></th>
<th>Siliq n=1,496</th>
<th>Stelara n=613</th>
<th>Placebo n=879</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>4 suicides</strong></td>
<td>4 suicides</td>
<td>0 suicides</td>
<td>0 suicides</td>
</tr>
</tbody>
</table>

### Serious side effects

**Serious infection**

- Over 12 weeks: 0.5% (Siliq), 0.3% (Stelara), 0.2% (Placebo)
- Over 52 weeks: 1.3% (Siliq), 1.0% (Stelara), 0.2% (Placebo)

**New onset of tuberculosis reactivation**: 1 person (Siliq), 0 people (Stelara), 0 people (Placebo)

**Other serious side effects**

<table>
<thead>
<tr>
<th>Side Effect</th>
<th>Siliq n=1,496</th>
<th>Stelara n=613</th>
<th>Placebo n=879</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arthralgia</td>
<td>5%</td>
<td>2%</td>
<td>3%</td>
</tr>
<tr>
<td>Headache</td>
<td>4%</td>
<td>4%</td>
<td>4%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>3%</td>
<td>3%</td>
<td>1%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>2%</td>
<td>1%</td>
<td>1%</td>
</tr>
<tr>
<td>Mouth or throat pain</td>
<td>2%</td>
<td>1%</td>
<td>1%</td>
</tr>
<tr>
<td>Myalgia</td>
<td>2%</td>
<td>1%</td>
<td>0.3%</td>
</tr>
<tr>
<td>Injection site reactions</td>
<td>2%</td>
<td>2%</td>
<td>1%</td>
</tr>
</tbody>
</table>

### Most common symptom side effects

<table>
<thead>
<tr>
<th>Side Effect</th>
<th>Siliq n=1,496</th>
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<th>Placebo n=879</th>
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<td>3%</td>
<td>3%</td>
<td>1%</td>
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<tr>
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<tr>
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<td>2%</td>
<td>1%</td>
</tr>
</tbody>
</table>
The Drug Facts Box: Improving the communication of prescription drug information

Lisa M. Schwartz1 and Steven Woloshin1

VA Outcomes Group, Department of Veterans Affairs Medical Center, White River Junction, VT 05009; The Dartmouth Institute for Health Policy and Clinical Practice, Geisel School of Medicine at Dartmouth, Lebanon, NH 03756; and Norris Cotton Cancer Center, Dartmouth Hitchcock Medical Center, Lebanon, NH 03756

Edited by Baruch Fischhoff, Carnegie Mellon University, Pittsburgh, PA, and accepted by the Editorial Board January 31, 2013 (received for review August 23, 2012)

Communication about prescription drugs ought to be a paragon of public science communication. Unfortunately, it is not. Consumers see $4 billion of direct-to-consumer advertising annually, which typically fails to present data about how well drugs work. The professional label—the Food and Drug Administration’s (FDA) mechanism to get physicians information needed for appropriate prescribing—may also fail to present benefit data. FDA labeling guidance, in fact, suggests that industry omit benefit data for new drugs in an existing class and for drugs approved on the basis of unfamiliar outcomes (such as depression rating scales). The medical literature is also problematic: there is selective reporting of favorable trials, favorable outcomes within trials, and “spinning” unfavorable results to maximize benefit and minimize harm. In contrast, publicly available FDA reviews always include the phase 3 trial data on benefit and harm, which are the basis of drug approval. However, these reviews are practically inaccessible: lengthy, poorly organized, and weakly summarized. To improve accessibility, we developed the Drug Facts Box: a one-page summary of benefit and harm data for each indication of a drug. A series of studies—including national randomized trials—demonstrates that most consumers understand the Drug Facts Box and that it improves decision-making. Despite calls from their own Risk Communication Advisory Committee and Congress (in the Affordable Care Act) to consider implementing boxes, the FDA announced it needs at least 3-5 years to make a decision. Given its potential public health impact, physicians and the public should not have to wait that long for better drug information.

Opponents, however, worry that the advertisements mostly increase inappropriate demand for marginally effective drugs.

Current investment in DTC advertising is substantial. Pharmaceutical companies spent more than $4 billion in 2011 on DTC advertisements (9), about 10 times FDA’s total budget for the evaluation of new drugs (10). In the United States, DTC advertisements are ubiquitous. The average American television watcher views about 15 h of them per year (11). DTC print advertisements appear in nearly every major US newspaper and magazine.

DTC advertising also influences physicians as do other marketing efforts such as advertisements in medical journals and detailing visits from pharmaceutical representatives. However, physicians mostly learn about prescription drugs from medical journal articles and other professional sources. None is more important than the FDA-approved drug label. Whether they realize it or not, physicians get information from the label all of the time. The Physicians Desk Reference is a compendium of labels, and popular electronic medical sources such as UpToDate reprint excerpts of the label.

In this paper, we will look at problems with how prescription drug information is presented to consumers and doctors. To illustrate these problems, we use the example of Abilify (aripiprazole), an antipsychotic drug most recently approved for the treatment of depression that is only partially responsive to another anti depressant (the drug is also approved for a variety of other disorders). Abilify—the fourth most heavily advertised drug in the United States (9)—had sales of more than $5 billion last year.
Suggestions for FDA: Communication of Benefit-Risk Summary and Assessment

1. Organize narrative with visually distinct, named sections

2. Include structured tables with trial descriptions and efficacy and side effect data
   - Basis of drug approval
   - Current treatment options
How do psoriasis treatments compare?

Medical review

Table 2: Comparative Response Rates for Psoriasis Biologics

<table>
<thead>
<tr>
<th></th>
<th>Etanercept (Enbrel©)</th>
<th>Infliximab (Remicade©)</th>
<th>Adalimumab (Humira©)</th>
<th>Ustekinumab (Stelara©)</th>
<th>Ixekizumab (Taltz©)</th>
<th>Secukinumab (Cosentyx©)</th>
<th>Brodalumab (Siliq©)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PASI 75</td>
<td>47%</td>
<td>79%</td>
<td>72%</td>
<td>72%</td>
<td>89%</td>
<td>78%</td>
<td>85%</td>
</tr>
<tr>
<td>PASI 100</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>37%</td>
<td>NA</td>
<td>41%</td>
</tr>
<tr>
<td>sPGA 0/1</td>
<td>51%&lt;sup&gt;a&lt;/sup&gt;</td>
<td>85%&lt;sup&gt;a&lt;/sup&gt;</td>
<td>63%&lt;sup&gt;a&lt;/sup&gt;</td>
<td>68%&lt;sup&gt;a&lt;/sup&gt;</td>
<td>82%</td>
<td>63%&lt;sup&gt;a&lt;/sup&gt;</td>
<td>79%</td>
</tr>
</tbody>
</table>

Source: Clinical Review of Data from PI.

<sup>a</sup> sPGA clear (0) or minimal (1)

<sup>b</sup> Secukinumab only included PASI 90 (56%)
Suggestions for FDA: Communication of Benefit-Risk Summary and Assessment

1. Organize narrative with visually distinct, named sections

2. Include structured tables with trial descriptions and efficacy and side effect data
   - Basis of drug approval
   - Current treatment options

3. Summarize FDA review team approval votes and rationale
<table>
<thead>
<tr>
<th>Division of Psychiatry Products</th>
<th>No</th>
<th>Reason Review (PDF)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Division of Cardiac and Renal Products</td>
<td>Yes</td>
<td>Reason Review (PDF)</td>
</tr>
<tr>
<td>Division of Epidemiology</td>
<td>No</td>
<td>Reason Review (PDF)</td>
</tr>
<tr>
<td>Division of Pharmacovigilance</td>
<td>Yes</td>
<td>Reason Review (PDF)</td>
</tr>
</tbody>
</table>
### Should FDA approve [Siliq] for moderate-to-severe plaque psoriasis?

**Primary FDA review:** Division of Dermatology and Dental Products

<table>
<thead>
<tr>
<th>Role</th>
<th>Decision</th>
<th>Reason</th>
</tr>
</thead>
<tbody>
<tr>
<td>Division Director</td>
<td>Yes</td>
<td>Reason Summary Review (PDF)</td>
</tr>
<tr>
<td>Team Leader</td>
<td>Yes</td>
<td>Reason Cross Discipline Team Leader Review (PDF)</td>
</tr>
<tr>
<td>Reviewer</td>
<td>No</td>
<td>Reason</td>
</tr>
</tbody>
</table>

..”the risk outweighs the benefits provided by this biologic. The safety signal for [suicidal ideation and behavior] requires further data to remediate the riskion.”

<table>
<thead>
<tr>
<th>Division</th>
<th>Decision</th>
<th>Reason</th>
</tr>
</thead>
<tbody>
<tr>
<td>Division of Psychiatry Products</td>
<td></td>
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<tr>
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<tr>
<td>Division of Epidemiology</td>
<td>No</td>
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</tr>
<tr>
<td>Division of Pharmacovigilance</td>
<td>Yes</td>
<td>Reason Review (PDF)</td>
</tr>
</tbody>
</table>
Routinely present agreement or disagreement to highlight whether important uncertainties exist

| Division Director | Yes | Reason Summary Review (PDF) |
| Team Leader | Yes | Reason Cross-Discipline Team Leader Review (PDF) |
| Reviewer | No |
| FDA consult reviews |
| Division of Psychiatry Products |
| Division of Cardiac and Renal Products | Yes | Reason Review (PDF) |
| Division of Epidemiology | No | Reason Review (PDF) |
| Division of Pharmacovigilance | Yes | Reason Review (PDF) |

“...that [Siliq] should be made available with labeling sufficient to describe and inform this risk, as well as a REMS with elements to assure safe use to insure that prescribers understand and acknowledge the risks, and document that patients who use [Siliq] are fully consented regarding the benefits and potential...
Suggestions for FDA:
Communication of Benefit-Risk Summary and Assessment

1. Organize narrative with visually distinct, named sections

2. Include structured tables with trial descriptions and efficacy and side effect data
   - Basis of drug approval
   - Current treatment options

3. Summarize FDA review team approval votes and rationale

4. Disseminate Benefit Risk Framework (with data tables) to prescribers and consumers

5. Expand/redesign FDA Drug Trial Snapshots for this purpose.
Drug Trials Snapshot: SILIQ for

DRUG TRIALS SNAPSHOT SUMMARY:

What is the drug for?
SILIQ is used for treatment of moderate to severe plaque psoriasis in adults.

- who may benefit from systemic treatment (such as injections or pills) or phototherapy (ultraviolet light treatment) and
- who did not respond or lost response to other systemic treatments.

How is this drug used?
SILIQ is an injection given under the skin once every week for the first three injections followed by an injection once every two weeks.

What are the benefits of this drug?
Clinical trials showed that SILIQ was better than a placebo in improving symptoms of plaque psoriasis and maintaining the improvement through a year of treatment.
What are the benefits of this drug (results of trials used to assess efficacy)?

The table below summarizes efficacy results for the clinical trials based on the two co-primary endpoints: 1) PASI 75, the proportion of subjects who achieved at least a 75% reduction in the Psoriasis Area and Severity Index (PASI) composite score that takes into consideration both the percentage of body surface area affected and the nature and severity of psoriatic changes (induration, erythema, and scaling) within the affected region, and 2) the proportion of subjects with a static Physicians Global Assessment (sPGA) score of 0 (clear) or 1 (almost clear), and at least a 2-point improvement from baseline. In Trials 2 and 3, comparisons were also made to ustekinumab for the primary endpoint of the proportion of subjects who achieved a reduction in PASI score of 100% (PASI 100) from baseline at Week 12.

Results are presented using efficacy or ITT (Intend to Treat) population.

Table 2. Efficacy Results at Week 12 in Adults with Plaque Psoriasis in Trials 1, 2, and 3; NRI

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Trial 1</th>
<th></th>
<th>Trial 2</th>
<th></th>
<th>Trial 3</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SILIQ</td>
<td>Placebo</td>
<td>SILIQ</td>
<td>Placebo</td>
<td>SILIQ</td>
<td>Placebo</td>
</tr>
<tr>
<td>PASI 75% response</td>
<td>185 (83)</td>
<td>6 (3)</td>
<td>528 (86)</td>
<td>210 (70)</td>
<td>531 (85)</td>
<td>217 (69)</td>
</tr>
<tr>
<td>PASI 100% response</td>
<td>93 (42)</td>
<td>1 (&lt;1)</td>
<td>272 (44)</td>
<td>65 (22)</td>
<td>229 (37)</td>
<td>58 (19)</td>
</tr>
<tr>
<td>sPGA success clear (0) or almost clear (1)</td>
<td>168 (76)</td>
<td>3 (1)</td>
<td>481 (79)</td>
<td>183 (61)</td>
<td>497 (80)</td>
<td>179 (57)</td>
</tr>
<tr>
<td>sPGA of clear (0)</td>
<td>93 (42)</td>
<td>1 (&lt;1)</td>
<td>274 (45)</td>
<td>65 (21)</td>
<td>229 (37)</td>
<td>58 (19)</td>
</tr>
</tbody>
</table>

Footnotes:
- NRI=non-responder Imputation
- Co-primary endpoints
Drug Trials Snapshot: SILIQ for Consumer & Prescribers

DRUG TRIALS SNAPSHOT SUMMARY:

What is the drug for?
SILIQ is used for treatment of moderate to severe plaque psoriasis in adults.

• who may benefit from systemic treatment (such as injections or pills) or phototherapy (ultraviolet light treatment) and

Why did FDA approve the drug?

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What are the benefits of this drug?
Clinical trials showed that SILIQ was better than a placebo in improving symptoms of plaque psoriasis and maintaining the improvement through a year of treatment.
Conclusion

FDA’s Benefit-Risk Assessments -- and review documents -- are a gold-mine.

- Independent, informed expert assessment of drug benefit and risk
- Explicit discussion of how (often difficult) approval decisions are made in the face of uncertainty

Dissemination efforts are important so prescribers and patients can make wiser decisions about drugs.
Session 3
Panel Discussion and Q&A

Sara Eggers
Facilitator

September 18, 2017
Open Public Comment

Graham Thompson
Office of Strategic Programs
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

September 18, 2017
Closing Remarks

Theresa Mullin, Ph.D.
Director, Office of Strategic Programs
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

September 18, 2017