U.S. FOOD & DRUG ADMINISTRATION

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

September 18, 2017

U.S. FOOD & DRUG ADMINISTRATION

Welcome

Graham Thompson
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

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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

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Session 1

Regulatory and Industry Experiences with Benefit-Risk Assessment Approaches

Graham Thompson
Facilitator

September 18, 2017

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Overview of FDA's Benefit-Risk Framework and its Implementation

Sara Eggers, Ph.D.
Decision Support and Analysis Team
Office of Programs and Strategic Analysis
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

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
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

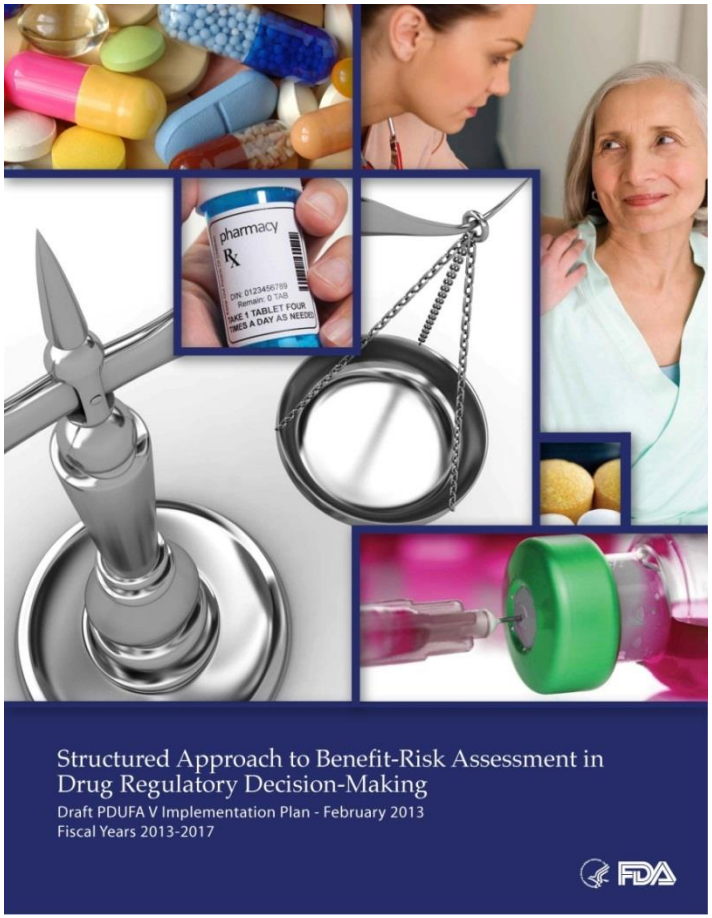
- Which safety concerns can be appropriately addressed through product labeling?
- Are there any serious safety concerns that may require risk management beyond labeling?
- How might multiple risk management elements fit together into a reasonable and appropriate strategy?

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

Feb 2013	Published Draft Implementation Plan
May 2013	CBER integrated the BRF into review templates for original biologics license applications (BLAs) and BLA efficacy supplements
Sept 2013	CDER established the Benefit-Risk Implementation Committee (BRIC) • Began process to revise clinical review and memo templates
Feb/May 2014	1st 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 • 2nd public meeting on Experiences with Benefit-Risk Assessment

Frameworks are starting to appear in posted reviews

(drug reviews are found at drugs@FDA)

Analysis of Condition	Schizophrenia 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.	Schizophrenia 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.
Current Treatment Options	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 a 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.
Benefit	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.	Although statistical superiority was substantiated for only one dose, there is no specific regulatory requirement that the efficacy of every labeled dosage must be shown with 2 trials. The Dosage and Administration section of labeling will sate a "target dose" recommendation that includes both 2 and 4 mg/day. In clinical practice, one should attempt to treat patients with the lowest effective dose and, clearly, for a proportion of subjects in these trials, 2 mg/day was effective.
Risk	In the overall development program, the most common TEAEs were weight increased, insomnia, headache, akathisia, somnolence, fatigue, anxiety, and increased appetite. With regard to potential risk for metabolic syndrome, in both MDD and schizophrenia trials, weight gain was more common and greater in the long-term trials. Elevated triglycerides were shown even in the short-term trials in both populations.	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

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Sara Eggers, Graham Thompson, Shanon Woodward

Benefit-Risk Implementation Committee
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Bob Temple, Ellis Unger, Susanne Walker

CDER and CBER leadership

CDER's Benefit-Risk Framework Regulatory Case Study

Mary T. Thanh Hai, MD
Office of New Drugs, Office of Drug Evaluation 2
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
September 18, 2017

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

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Adapted from Dr. Sara Eggers' presentation

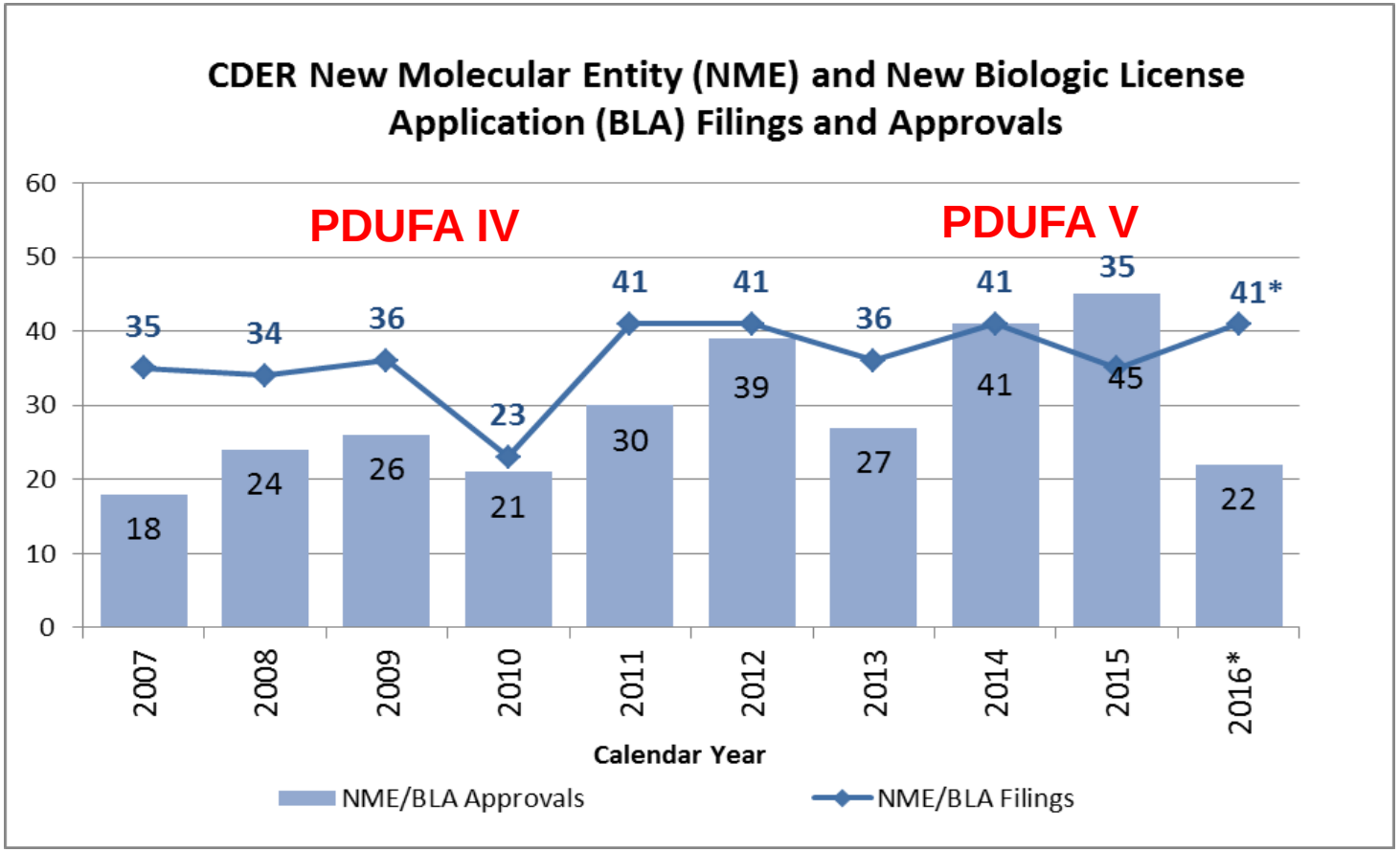
Liraglutide as Case Study 1

- 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 liraglutide 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



Source: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugInnovation/ucm534863.htm

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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Nusinersen as Case Study 2

- 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**

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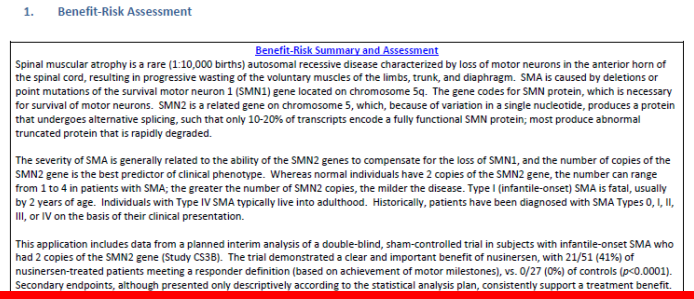
Nusinersen as Case Study 2



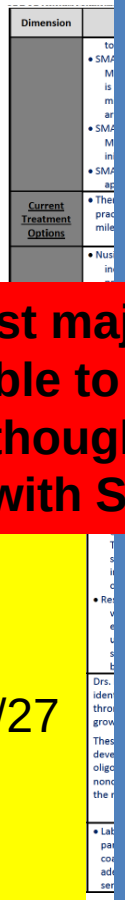
1. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Spinal muscular atrophy is a rare (1:10,000 births) autosomal recessive disease characterized by loss of motor neurons in the anterior horn of the spinal cord, resulting in progressive wasting of the voluntary muscles of the limbs, trunk, and diaphragm. SMA is caused by deletions or point mutations of the survival motor neuron 1 (SMN1) gene located on chromosome 5q. The gene codes for SMN protein, which is necessary for survival of motor neurons. SMN2 is a related gene on chromosome 5, which, because of variation in a single nucleotide, produces a protein that undergoes alternative splicing, such that only 10-20% of transcripts encode a fully functional SMN protein; most produce abnormal truncated protein that is rapidly degraded.

The severity of SMA is generally related to the ability of the SMN2 genes to compensate for the loss of SMN1, and the number of copies of the SMN2 gene is the best predictor of clinical phenotype. Whereas normal individuals have 2 copies of the SMN2 gene, the number can range from 1 to 4 in patients with SMA; the greater the number of SMN2 copies, the milder the disease. Type I (infantile-onset) SMA is fatal, usually by 2 years of age. Individuals with Type IV SMA typically live into adulthood. Historically, patients have been diagnosed with SMA Types 0, I, II, III, or IV on the basis of their clinical presentation.

This application includes data from a planned interim analysis of a double-blind, sham-controlled trial in subjects with infantile-onset SMA who had 2 copies of the SMN2 gene (Study CS3B). The trial demonstrated a clear and important benefit of nusinersen, with 21/51 (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.



Dimension

Current Treatment Options

(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.

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

(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.

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.

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

ERG

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

Approach

- 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

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)

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

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

Format

- Most interviewees felt that:
  - ✓ BRF format is effective in organizing and presenting content
  - ✓ BRF format helps makes 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

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

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

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.

M4E(R1) Section 2.5.6

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 biopharmaceutics, 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 clarify 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 concerns have 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 conceived by the Vancouver Group and was published in 1979.

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)

Acknowledgement to Francesco Pignatti, EMA & M4E EWG member

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

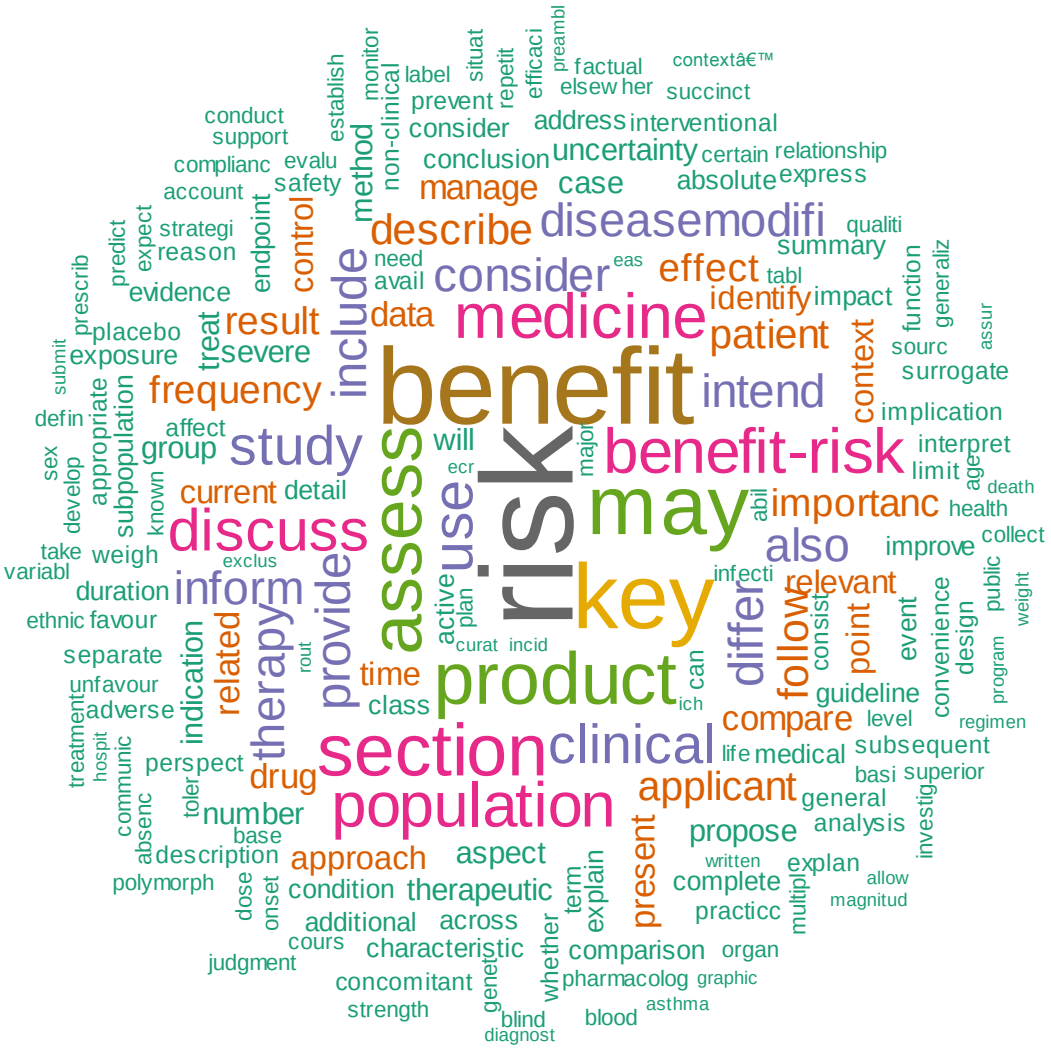
Notable aspects of M4E revision: 2.5.6.4 Benefit-Risk Assessment, cont.

- 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

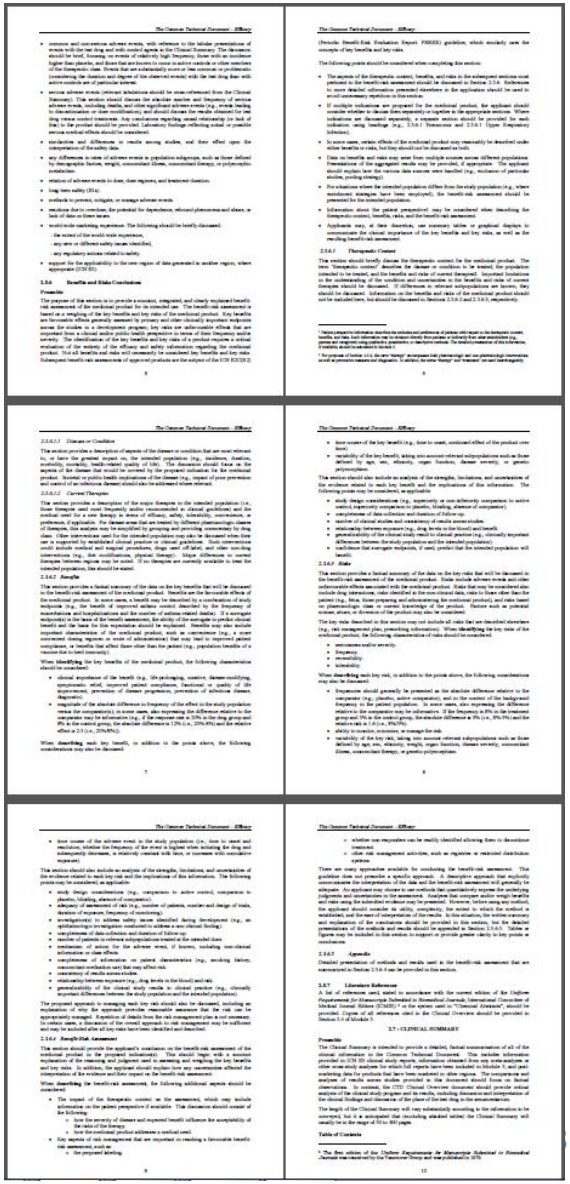
Moving from M4E(R1) to M4E(R2)…



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



U.S. FOOD & DRUG ADMINISTRATION

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


FDA
U.S. FOOD & DRUG
ADMINISTRATION

U.S. FOOD & DRUG ADMINISTRATION

BREAK

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

EMA framework for benefit-risk assessment

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

Francesco Pignatti, European Medicines Agency (EMA)

Contents

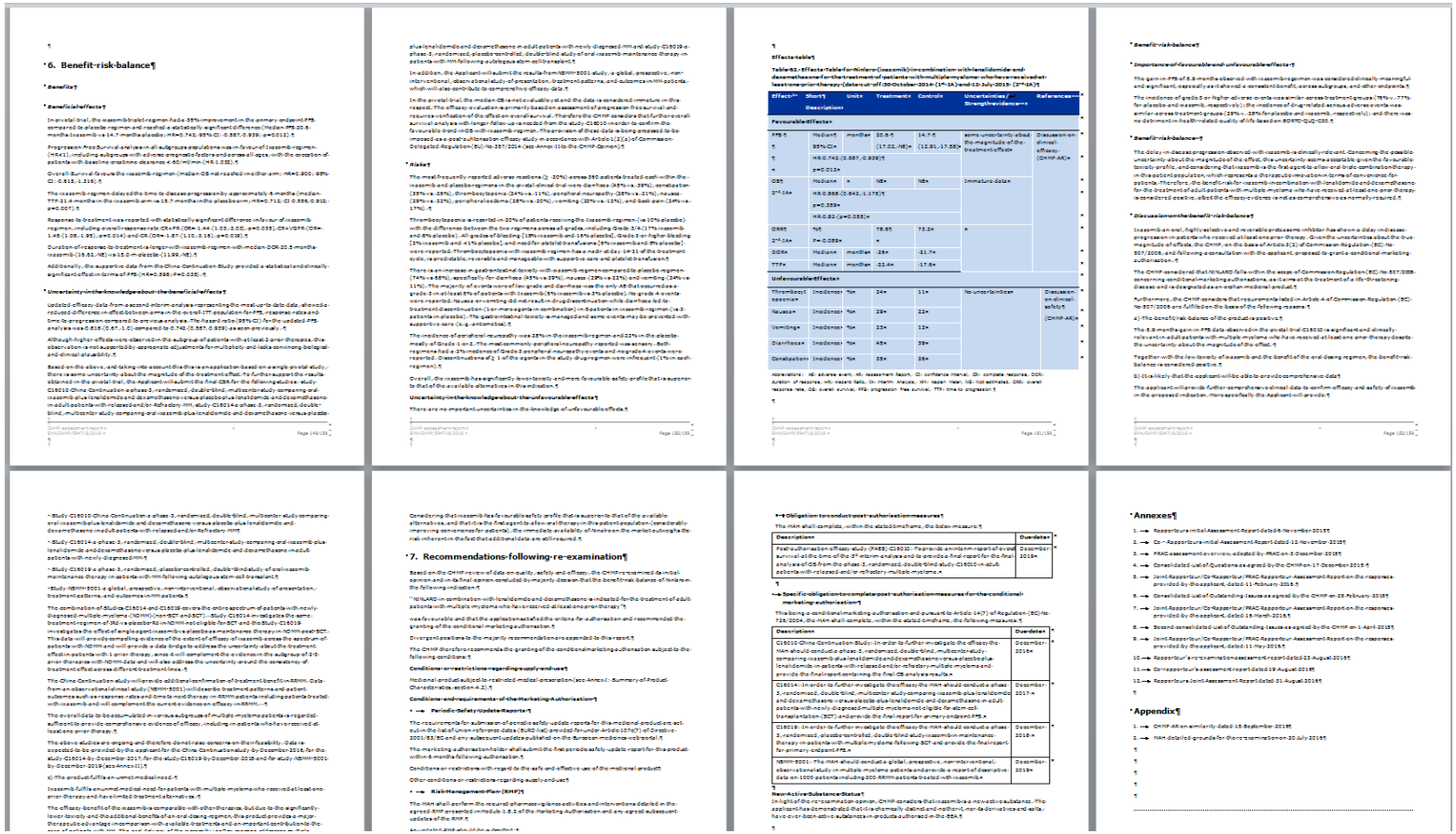
- From "quality, safety and efficacy" to benefit-risk assessment
- EMA framework for benefit-risk assessment
- Quantitative methods: Are we ready?
- Patient preferences; uncertainties
- Conclusions, perspective

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)



http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/003844/WC500217623.pdf

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

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

Daniels N. Accountability for reasonableness. *BMJ*. 2000

Eichler HG, et al. Fifty years after thalidomide; what role for drug regulators? *Br J Clin Pharmacol*. 2012

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***

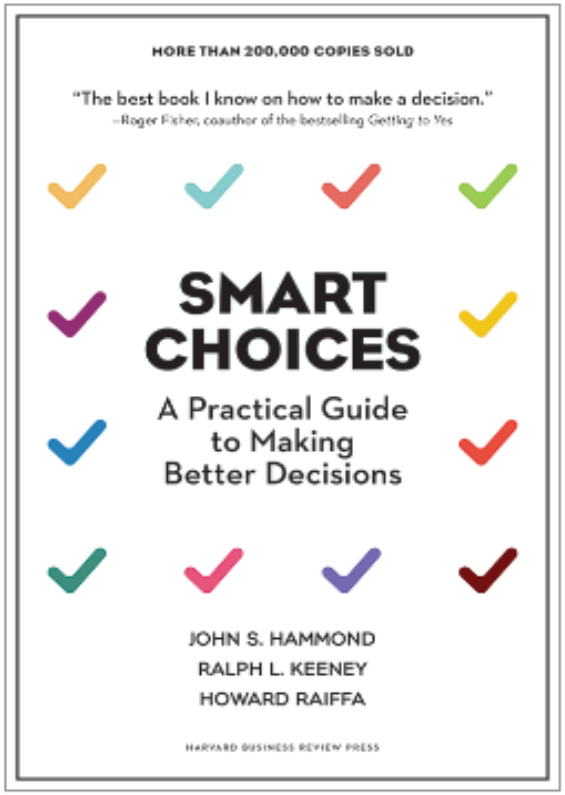
2004/27/EC

The **risk-benefit balance** is not considered to be favourable

Therapeutic efficacy is insufficiently substantiated

Benefit-Risk: A decision problem

- **Pr**oblem: Is Benefit-Risk balance positive?
- **O**bjective: Goal of therapy? Attributes
- **A**lternatives
  - Approve; reject; (reframe, e.g., restrict indication)
- **C**onsequences of alternatives
  - Estimated based on data
- **T**rade-offs
  - Based on value judgments
- **U**ncertainties (and how to cope with them)
- **R**isk-attitude and **L**inked decisions



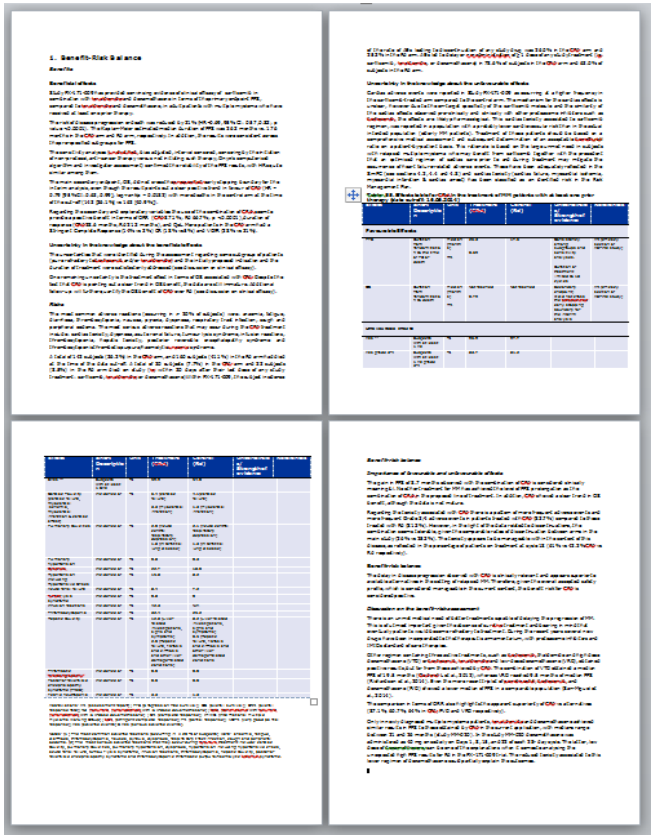
J Hammond *et al*. (1999) Smart Choices: A Practical Guide to Making Better Decisions

EMA Benefit-Risk Assessment Template

- Benefits
  - Beneficial effects
  - Uncertainty
- Risks
  - Unfavourable effects
  - Uncertainty

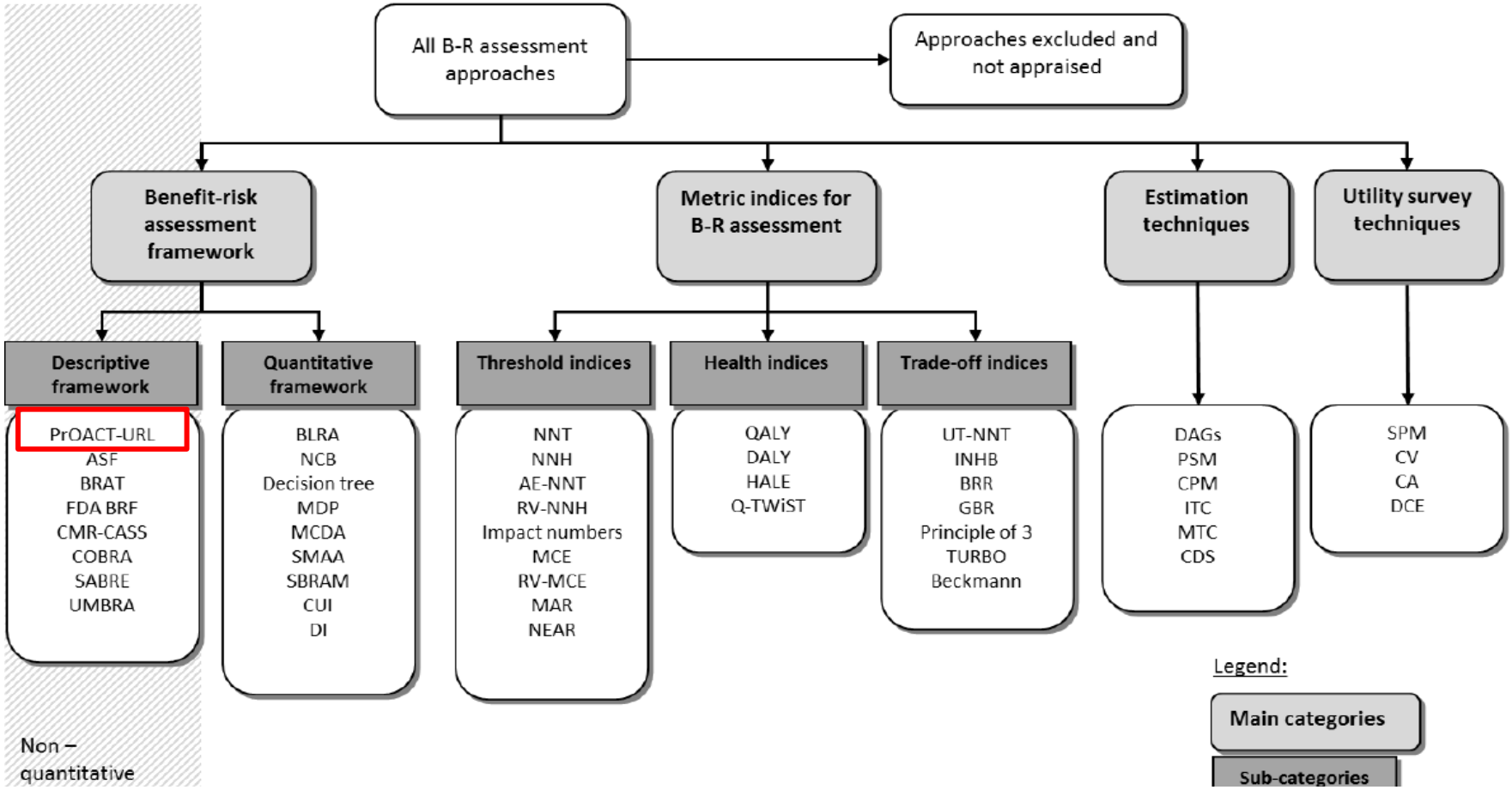
Effects Table

- Importance of effects
- Benefit-risk balance



Structured benefit-risk assessment

Benefit-risk assessment toolkit



Quantitative methods: Are we ready?

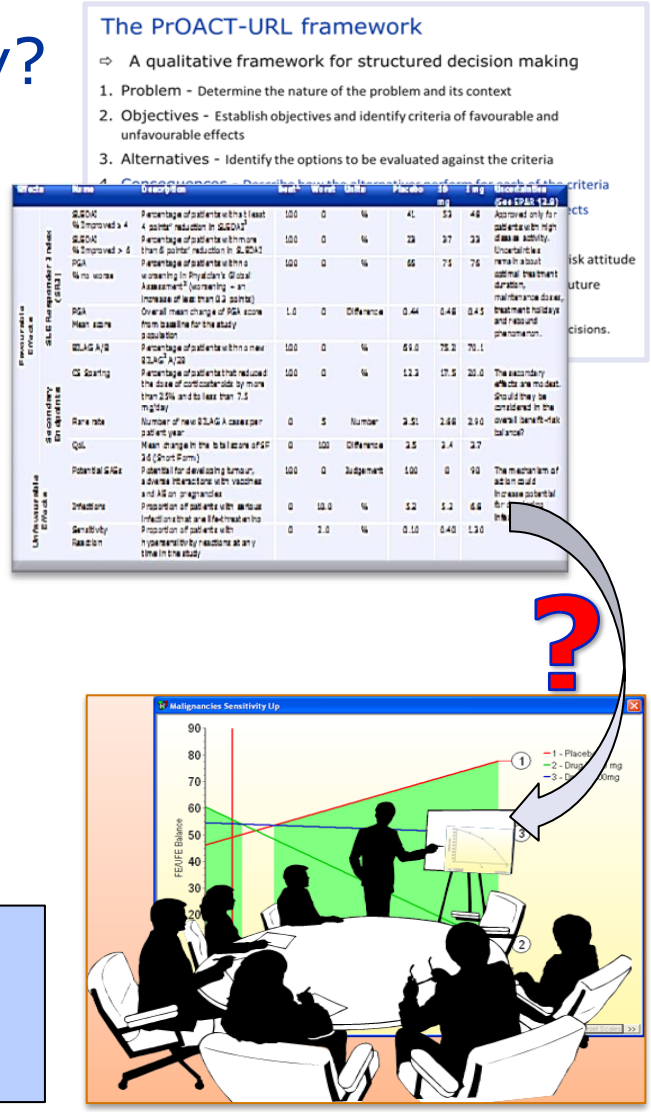
Different opinions for and against

Complex regulatory environment, unlikely to change.

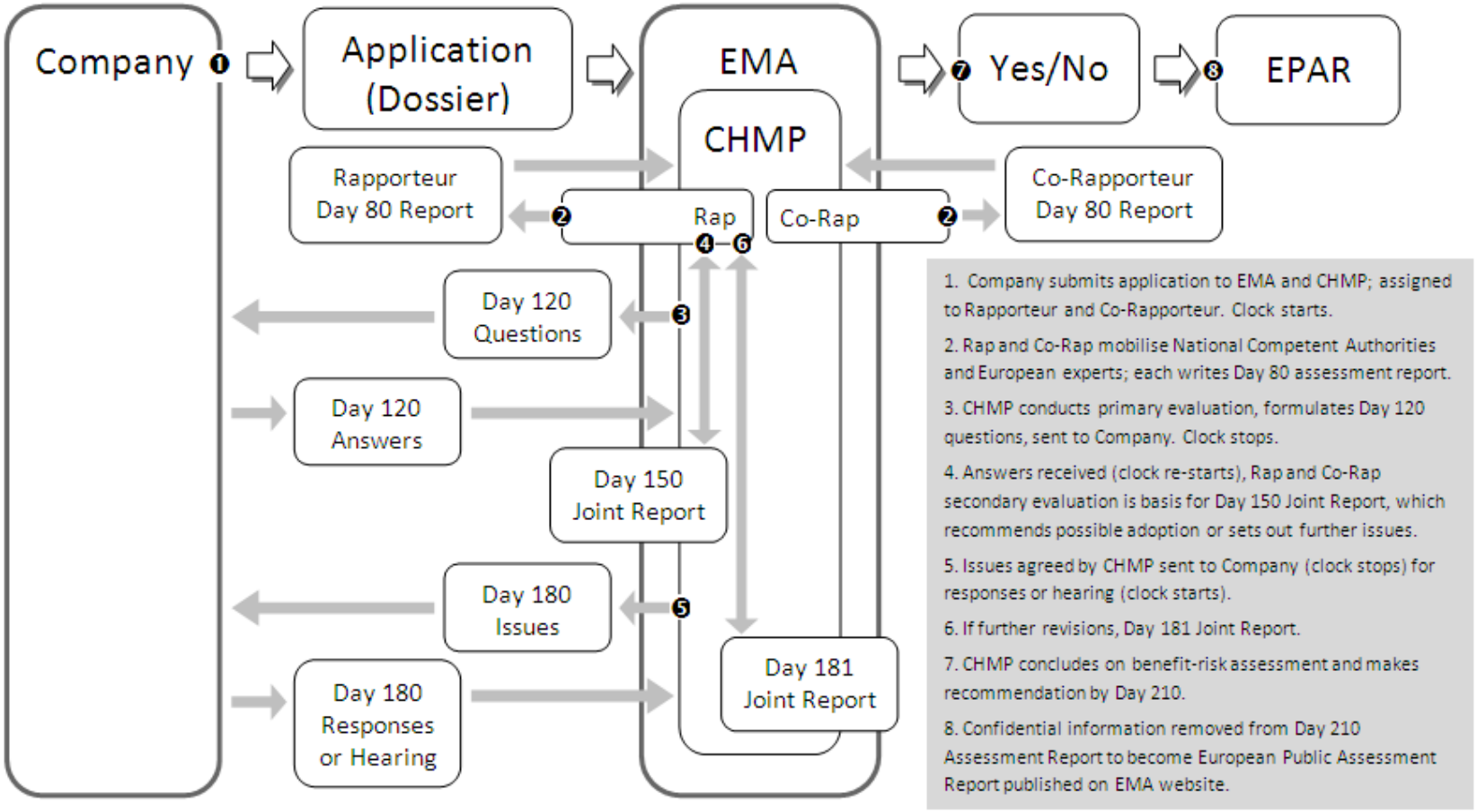
May be useful as communication tool:

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

Role of quantitative approaches currently unclear for reviewers



Complexity of our process



Phillips, L. D., Fasolo, B., Zafiropoulos, N., & Beyer, A. (2011). Is quantitative benefit-risk modelling of drugs desirable or possible? *Drug Discovery Today: Technologies*

Different views about quantitative methods

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

Pignatti, F., et al. (2015). Clin Pharmacol Ther 98(5): 522-533.

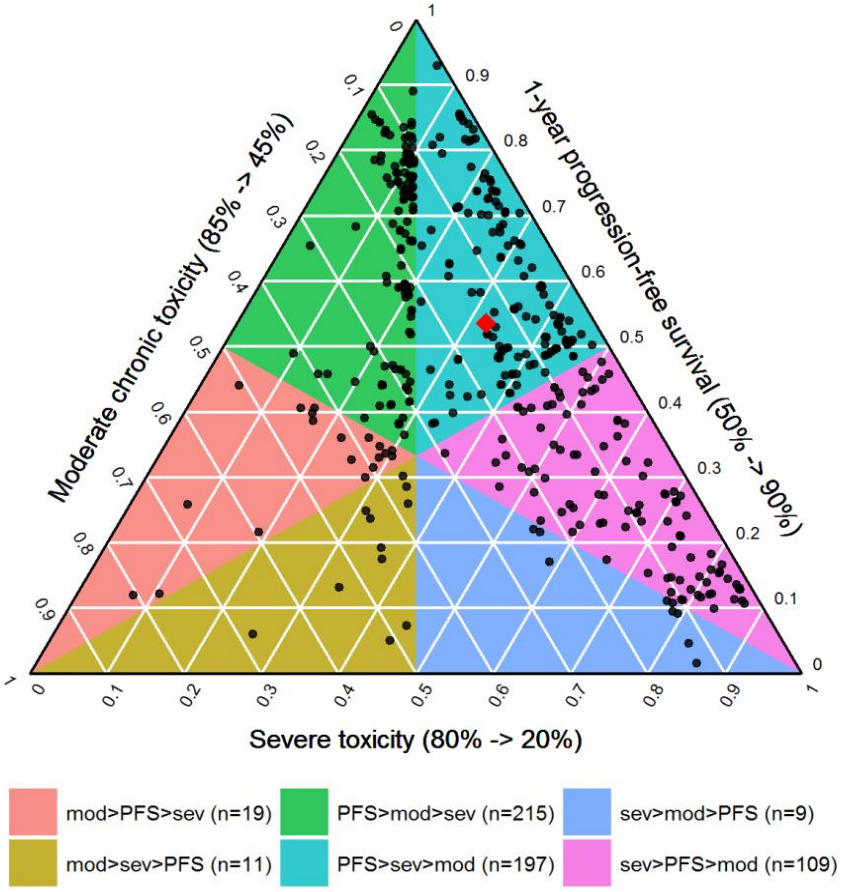
Weighing benefits and risks

- 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[1]

[1]FDA CDRH Guidance (2016) Patient Preference Information – Voluntary Submission, Review in Premarket Approval Applications, Humanitarian Device Exemption Applications, and De Novo Requests, and Inclusion in Decision Summaries and Device Labeling. http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-meddev-gen/documents/document/ucm446680.pdf

EMA Framework of interaction with patients

- 2014 revised framework of EMA interaction with patients[1]
- 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



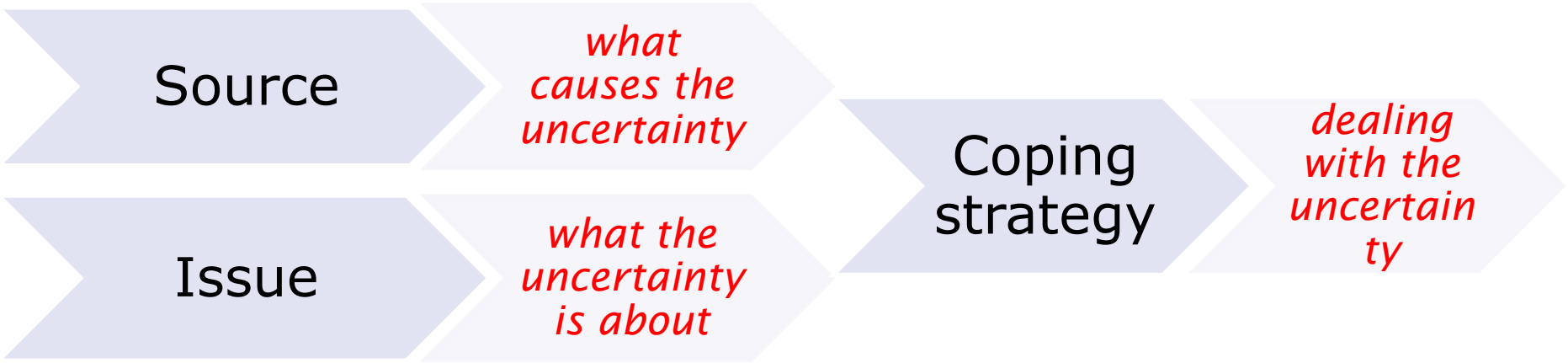
(1) http://www.ema.europa.eu/docs/en_GB/document_library/Other/2009/12/WC500018013.pdf

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



Lipshitz R. and Strauss O. (1997) Coping with uncertainty: A Naturalistic Decision-Making Analysis. *Org. Behav. Human Dec. Proc.* (69) pp. 149-163.

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

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

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

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"

EUROPEAN MEDICINES AGENCY

Thank you

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francesco.pignatti@ema.europa.eu

FDA workshop - September 18, 2017

Public Meeting on Benefit-Risk Framework Implementation

swissmedic

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

Claus Bolte, MD MBA – Sector Head Marketing Authorization

swissmedic

Outline & Context

- **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)

Established in 1871
SMW Swiss Medical Weekly
Formerly: Schweizerische Medizinische Wochenschrift
The European Journal of Medical Sciences

Review article: Current opinion | Published 13 March 2015, doi:10.4414/smw.2015.14120
Cite this as: Swiss Med Wkly. 2015;145:w14120

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.

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Context

Interconnected world – post-trust Society

Social Media & Transparency

Medical need grows faster than healthcare budgets

Empowered patients

Personalized, Stratified, Precision Medicine

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

New facilitated (expedited) licensing pathways

Pediatric (& Geriatric) Data

New trial designs; RCT : RWD

Data Exclusivity

Master protocols, basket trials

REVISION OF M4E GUIDELINE ON ENHANCING THE FORMAT AND STRUCTURE OF BENEFIT-RISK INFORMATION IN ICH

EFFICACY - M4E(R2)

2.5.6.4 Benefit-Risk Assessment

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,

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Benefit : Risk or Benefit-Harm-Uncertainty

(Evaluate the probability to benefit or harm)

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.

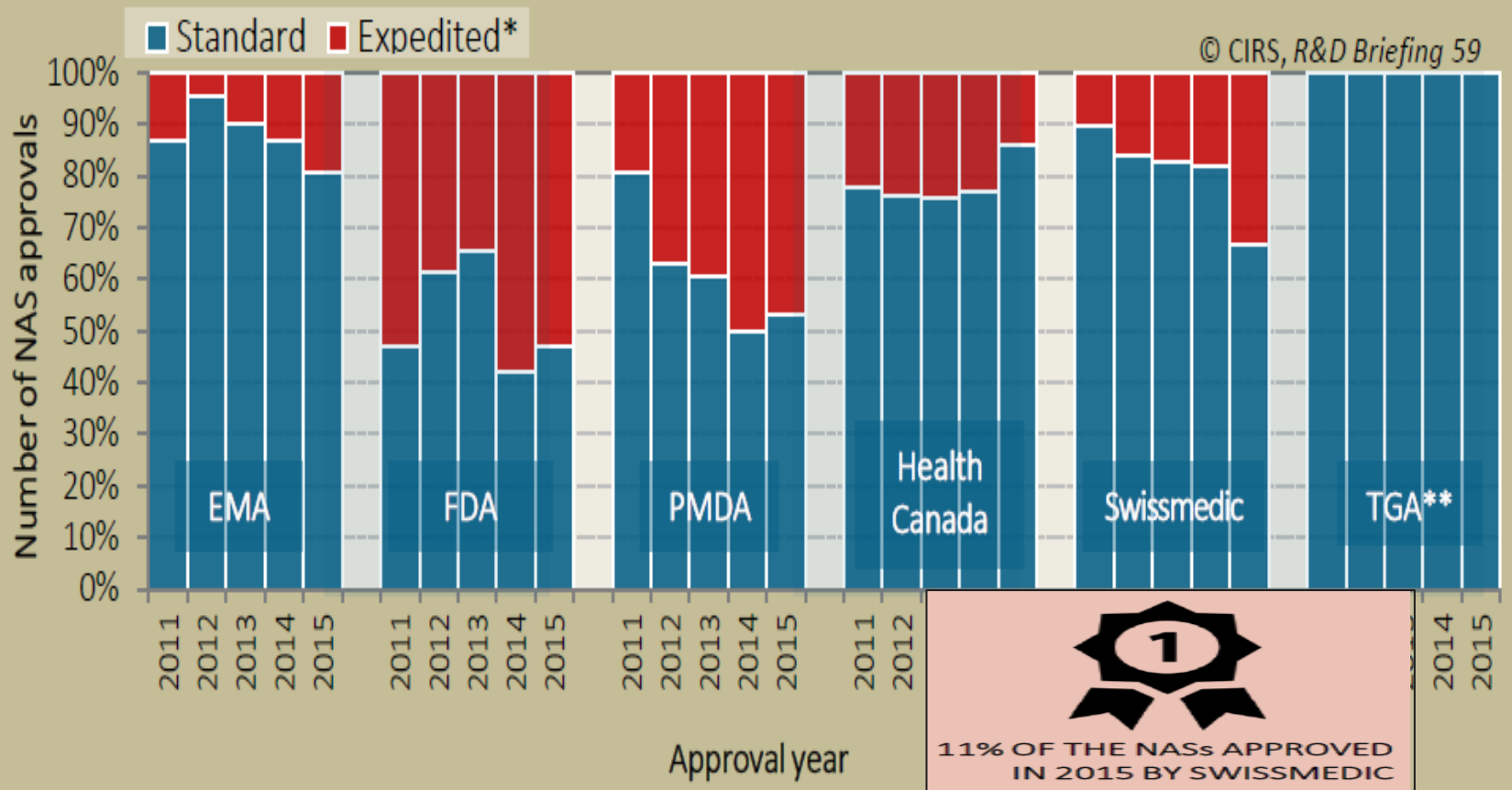
➢**Authorisation does not mean that a drug cannot harm an *individual patient***

➢**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.**

Characteristics: Review type

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/PM Review'.

**TGA does not currently have an expedited evaluation progra

1

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

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Network(ed)

ICH
harmonisation for better health

i-p-r-f.org
International Pharmaceutical Regulators Forum

IGDRP
International Generic Drug Regulators Pilot

World Health Organization

ACSS Consortium
Australia-Canada-Singapore-Switzerland Consortium
Australian Government Department of Health Therapeutic Goods Administration · Health Canada · Santé Canada · HSA · swissmedic

OECD
BETTER POLICIES FOR BETTER LIVES

PIC/S

EUPATI
European Patients' Academy on Therapeutic Innovation

Council of Europe
COUNCIL OF EUROPE · CONSEIL DE L'EUROPE

Summary and Proforma Template for the Benefit-Risk Assessment of Medicines

CIRS Centre for Innovation in Regulatory Science

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

Compound Identifier(s):
Product name: Brand name / Generic name:
Active Ingredient(s)/ Strength(s)/ Dosage form:
Proposed Indication:

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 exercise 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

Quick Links

Print Full Form | Email Full Form | View Full Form
Print Summary | Email Summary | View Summary

Contents | Background | Overall Summaries | Identified B&R | B&R Study Info | Weights & Values | Visualisation | Conclusions | B&R Summary

CIRS Centre for Innovation in Regulatory Science

Product Name:

Indication:

PROFORMA SECTION

Table of Contents

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.

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

Example

	Evidence	Uncertainties	Conclusions
Dose finding (CPR)	DCV + pegIFNα/RBV but not for DCV in combination with SOF	DCV + SOF	Acceptable since DCV/SOF is efficacious and safe.
Interaction potential (CPR)	• Extensive DDI study program		DDI with CYP3A4 inducers and inhibitors → **Contraindication** for strong inducers and dose adjustment for CYP3A inhibitors and moderate inducers. DDIs comparable to LDV and clearly better than under all PIs.
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 the 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** • **HBV/HCV** • **Hepatic impairment and decompensated liver disease** • **Liver transplant** • **Patients >65 years**	• No unexpected AEs → acceptable safety profile • PK: hepatic impairment → AUC↓ • PK: renal impairment → AUC↑ • PK: BMI no significant effect
Pre-clinical safety data (PCR)	• Hepatic and adrenal gland effects at exposures similar to clinical AUC. • In dogs bone marrow toxicity at 9-fold the clinical AUC.		• No safety signals in humans
DCV/SOF	GT-1, treatment naive w/o cirrhosis		limitations of the "pivotal" phase 2 study but compelling results: (+)
	GT-1, TVR/BOC treatment failure		24 weeks R: (+) 12 weeks R: (-)
	GT-1, compensated cirrhosis		very limited clinical data → **B/R assessment is not possible**: (-)
	GT-3		Insufficient clinical data → **B/R assessment is not possible**: (-)
	GT-4		no clinical data → **B/R assessment is not possible**: (-)
DCV/pegIFNα/RBV	GT-4		pivotal phase 3 study **supports proposed indication**: (+)

BMJ 2017;357:j2460 doi: 10.1136/bmj.j2460 (Published 2017 May 24)

FEATURE

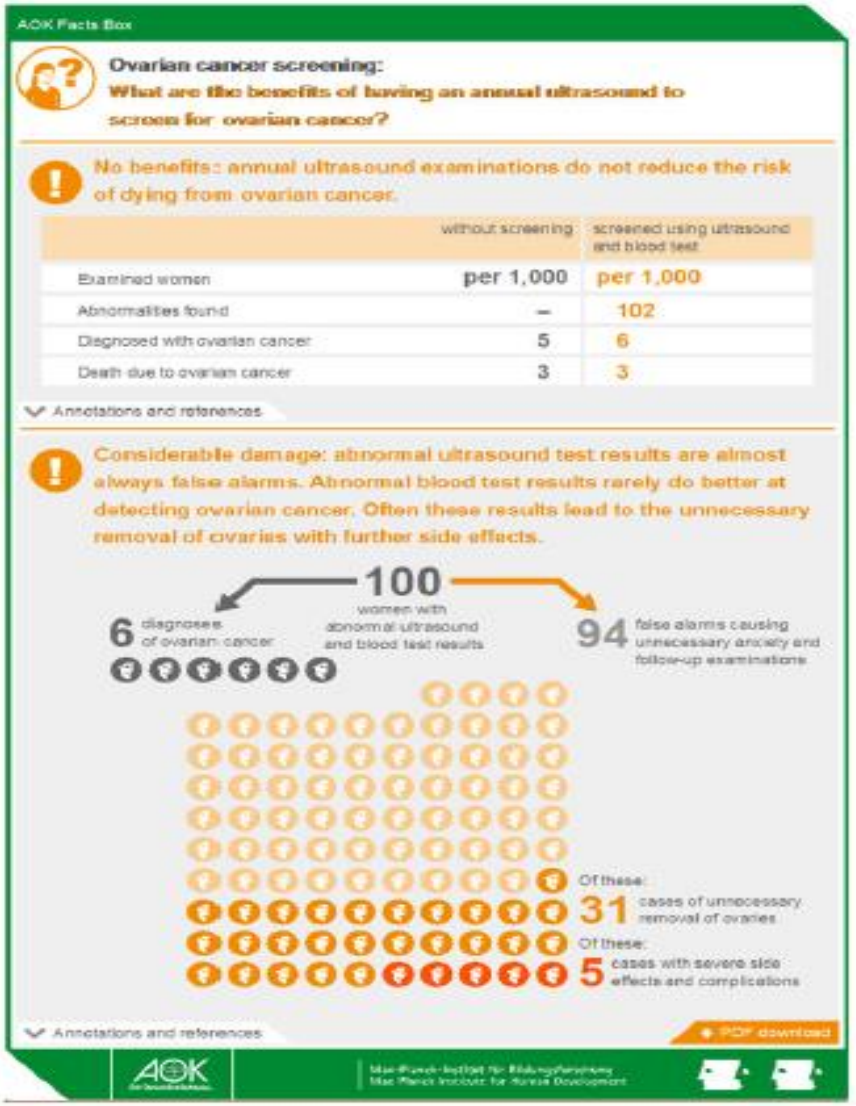
How new fact boxes are explaining medical risk to millions

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 *director*[1], Kai Kolpatzik *head*[2]

[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.[1] Instead they get persuasion, marketing, and, in some countries, misleading direct-to-consumer advertising.[2 3]

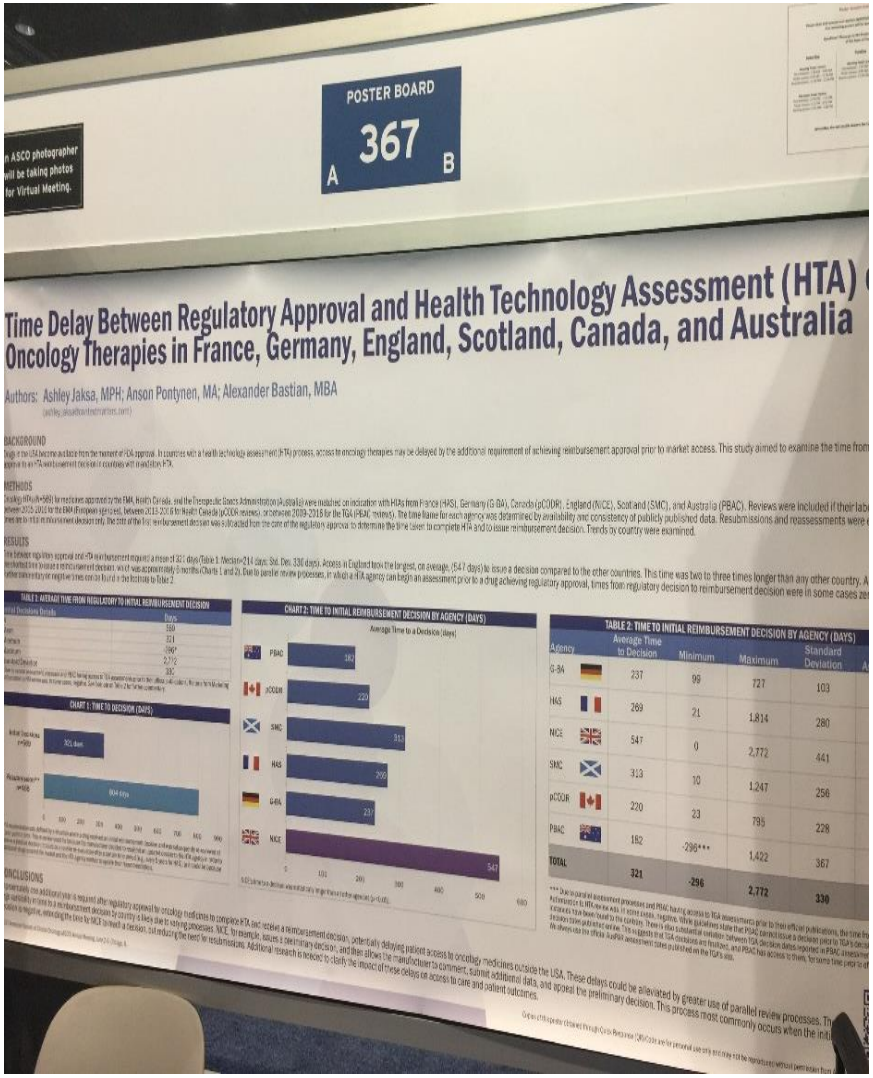


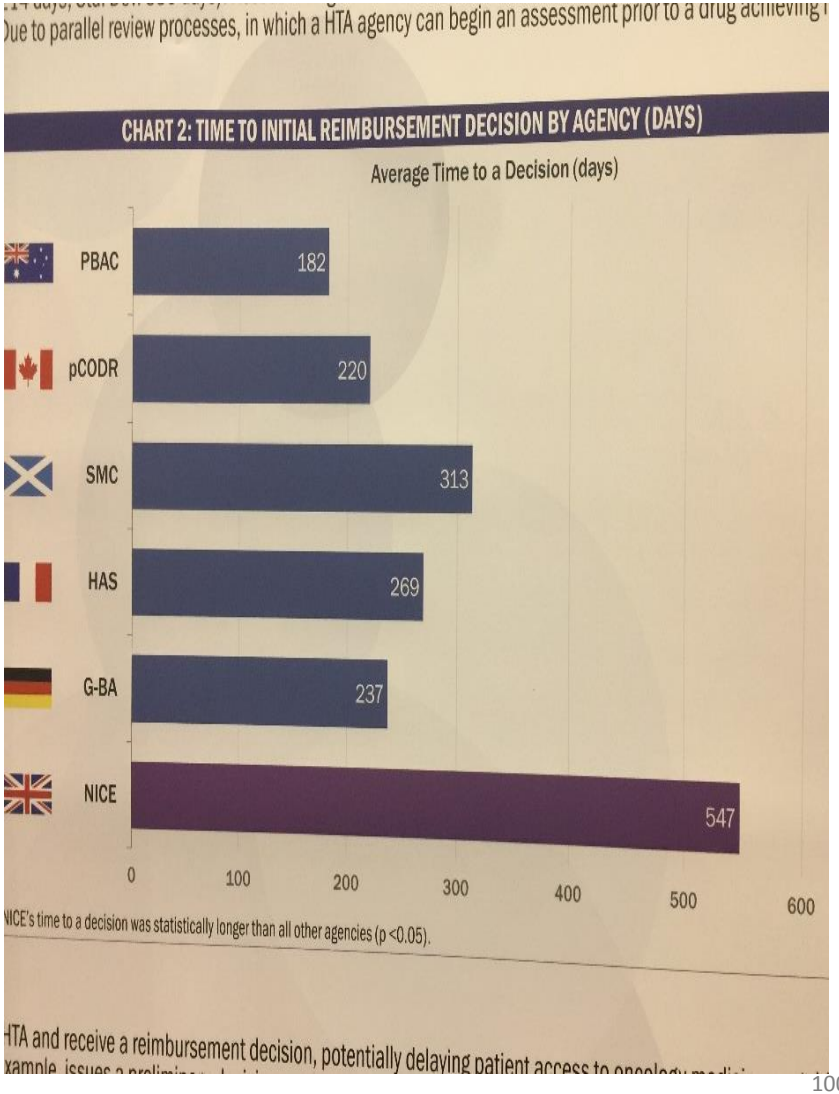
Assembling the data

In general, fact boxes report the results from a randomised trial or, if available, a systematic review; provide quantitative, evidence based information about benefits and harms; use absolute numbers rather than relative risk reductions or other formats that are known to confuse patients and physicians; and

swissmedic

Market Access = Regulatory + HTA





Outlook

TABLE 1. Selected Value Frameworks Developed for Patients With Cancer

	ASCO Value Framework	NCCN Value Pathways	ESMO MCB Scale	ICER Value Assessment	MSKCC DrugAbacus
Target Audience	Doctor, patient	Doctor, patient	Payer, policy maker	Payer, policy maker	Payer, policy maker
Evidence	Pivotal trials	Broad	Mainly phase II and III comparative trials	Broad	Pivotal trials
Efficacy	OS, PFS, RR, TFS	OS, PFS	OS, PFS	Varies; usually QALYs	OS
Indirect Loss (Productivity)	No	No	No	No	No
Toxicity	Yes	Yes	Yes	Yes	Yes
QOL/Palliation	Yes	No	Yes	Yes	No
Patient Preference	No	No	No	No	No
Cost	Displayed	Part of calculation	Displayed	No	Displayed
Patient Cost	Drug copay	No	No	Maybe	No
Medical Cost Offsets	No	No	No	Yes	No
Methodology	New	New	New	New and old	New
Outcome	Net health benefit scale (20–130), drug cost	Score 1–5 on each of five evidence blocks	Graded 1–4	Value-based price	Value-based price
Use of Real-World Data	No	Yes	No	Yes	No
Patient Perspective	No	Yes	No	Yes	No

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

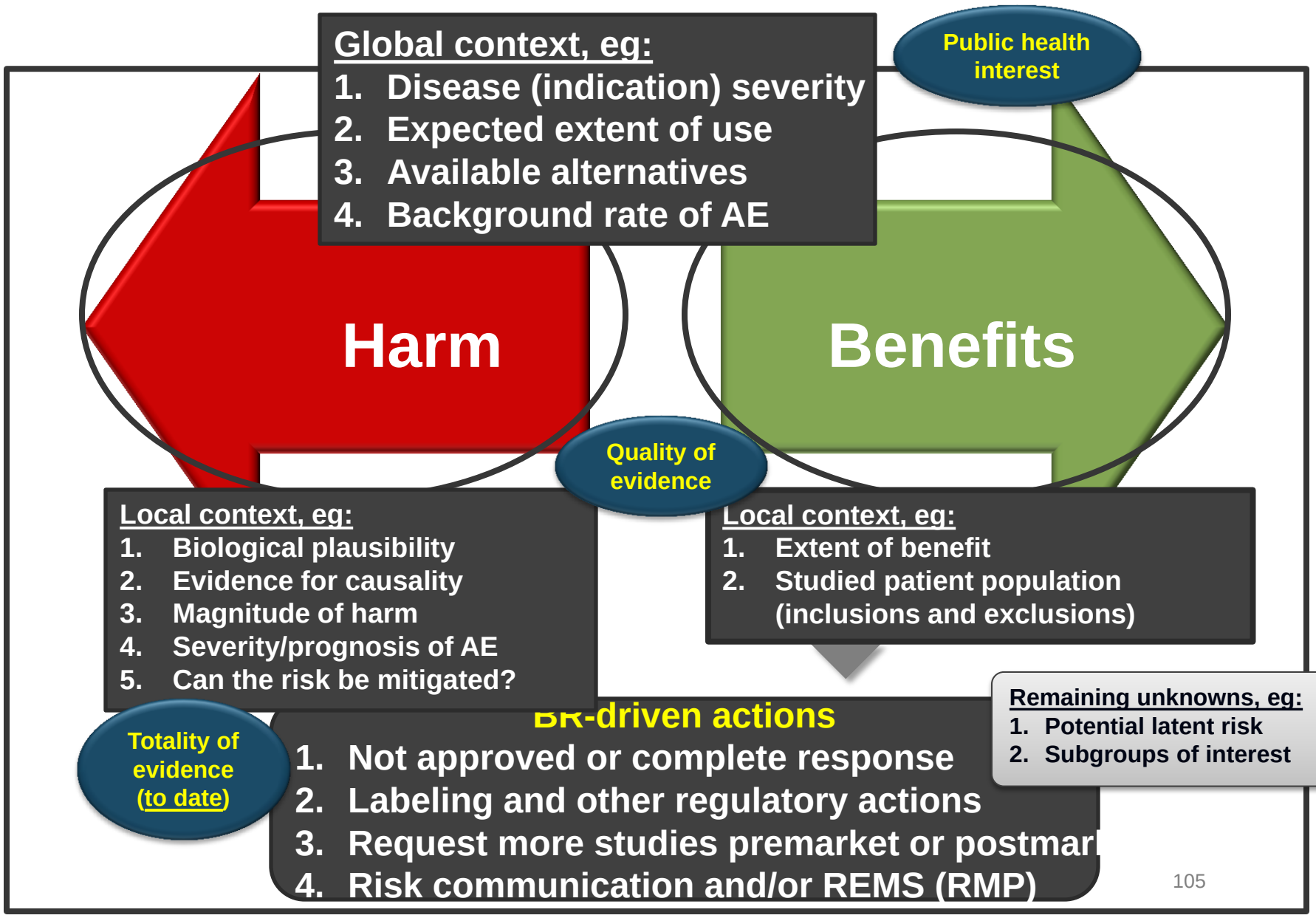
Disclaimer

- **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.**

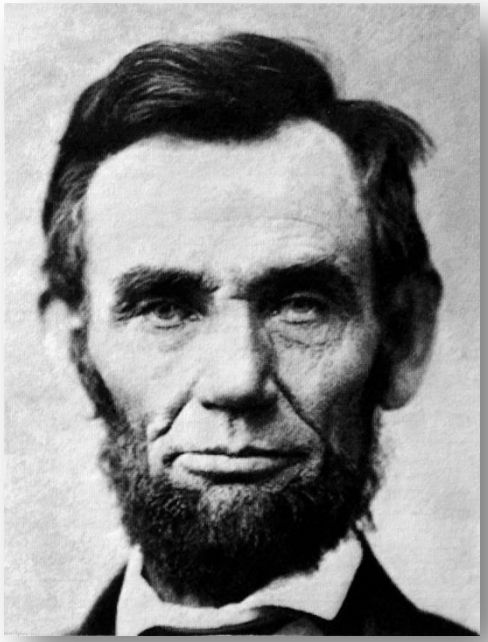
Outline

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



"The best way to predict your future is to create it!"



Abraham Lincoln

The 16th President of the United States, 1861

EWG M4E (R2), Lisbon, June 2016

In Summary: Notable Aspects of The Revised Guidance

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**

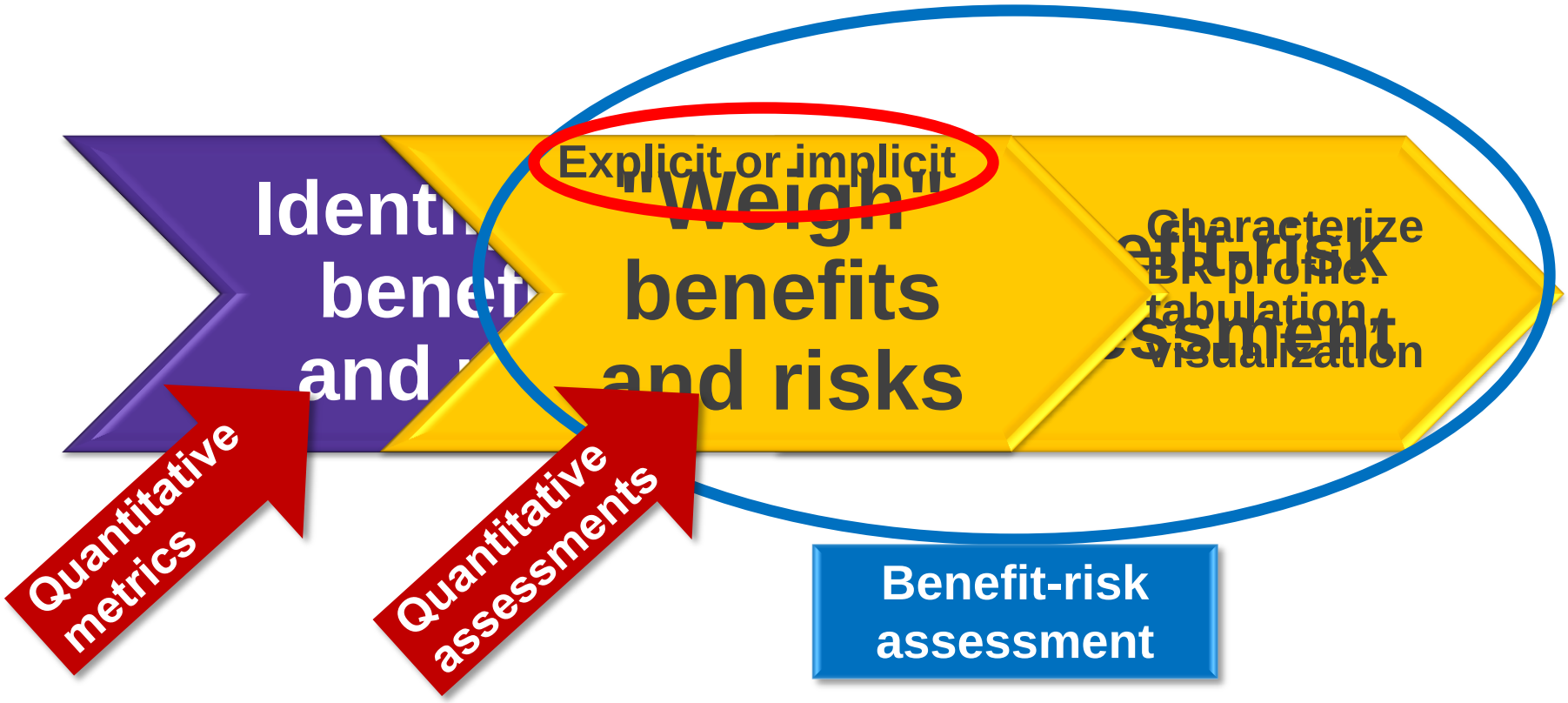
3. **An applicant may choose to use methods that quantitatively express the underlying judgments and uncertainties in the assessment. Analyses that compare and/or weigh benefits and risks using the submitted evidence may be presented**
4. **Written to be consistent with regulatory post-marketing requirements (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

Logical Components of Evaluating BR Profiles



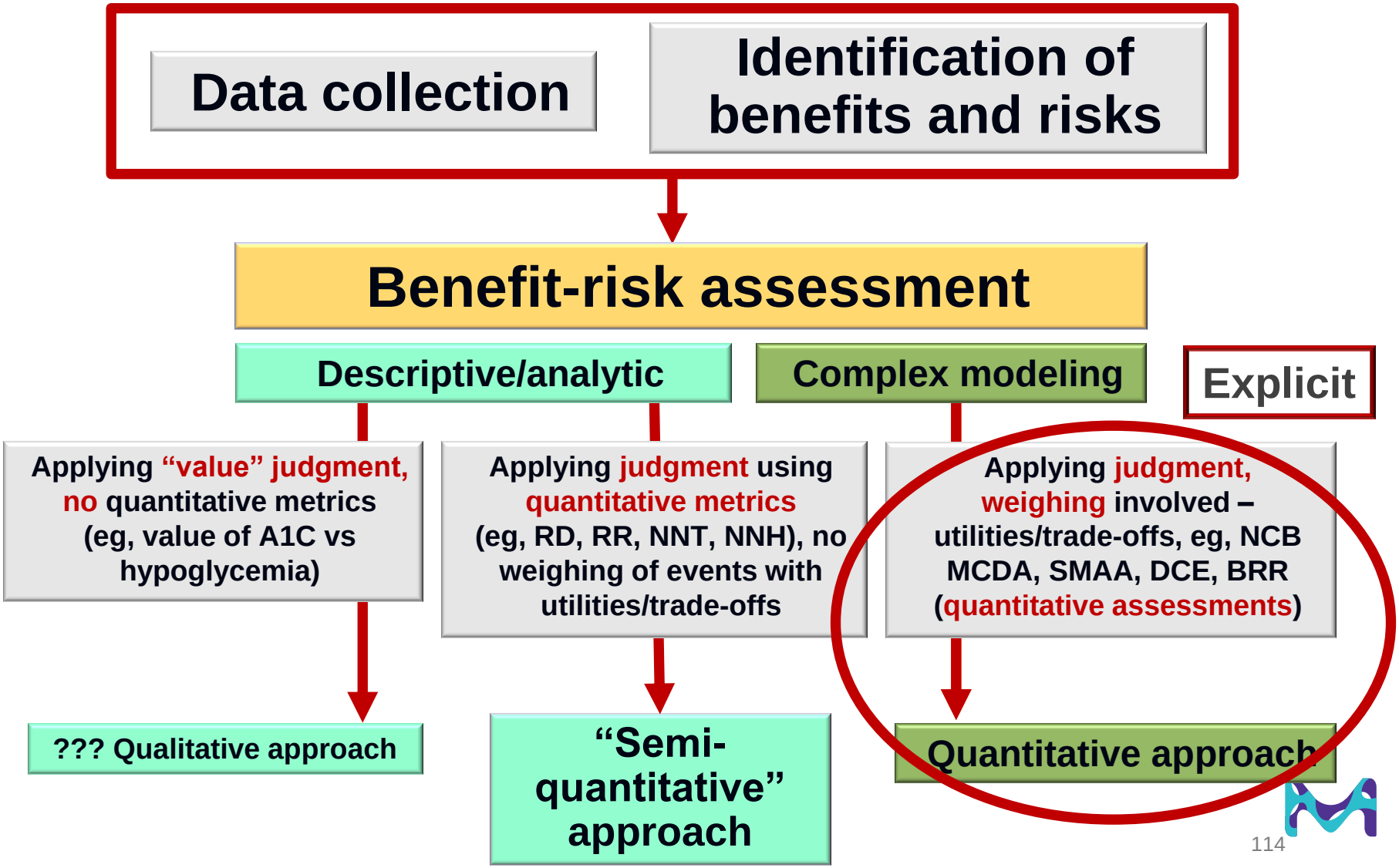
Weighing of Benefits and Risks Can Be Explicit or Implicit…

What does "explicit" weighing entail?

The Age-Old Question…

Qualitative vs Quantitative Assessments

Quantitative Metrics vs Quantitative Assessments



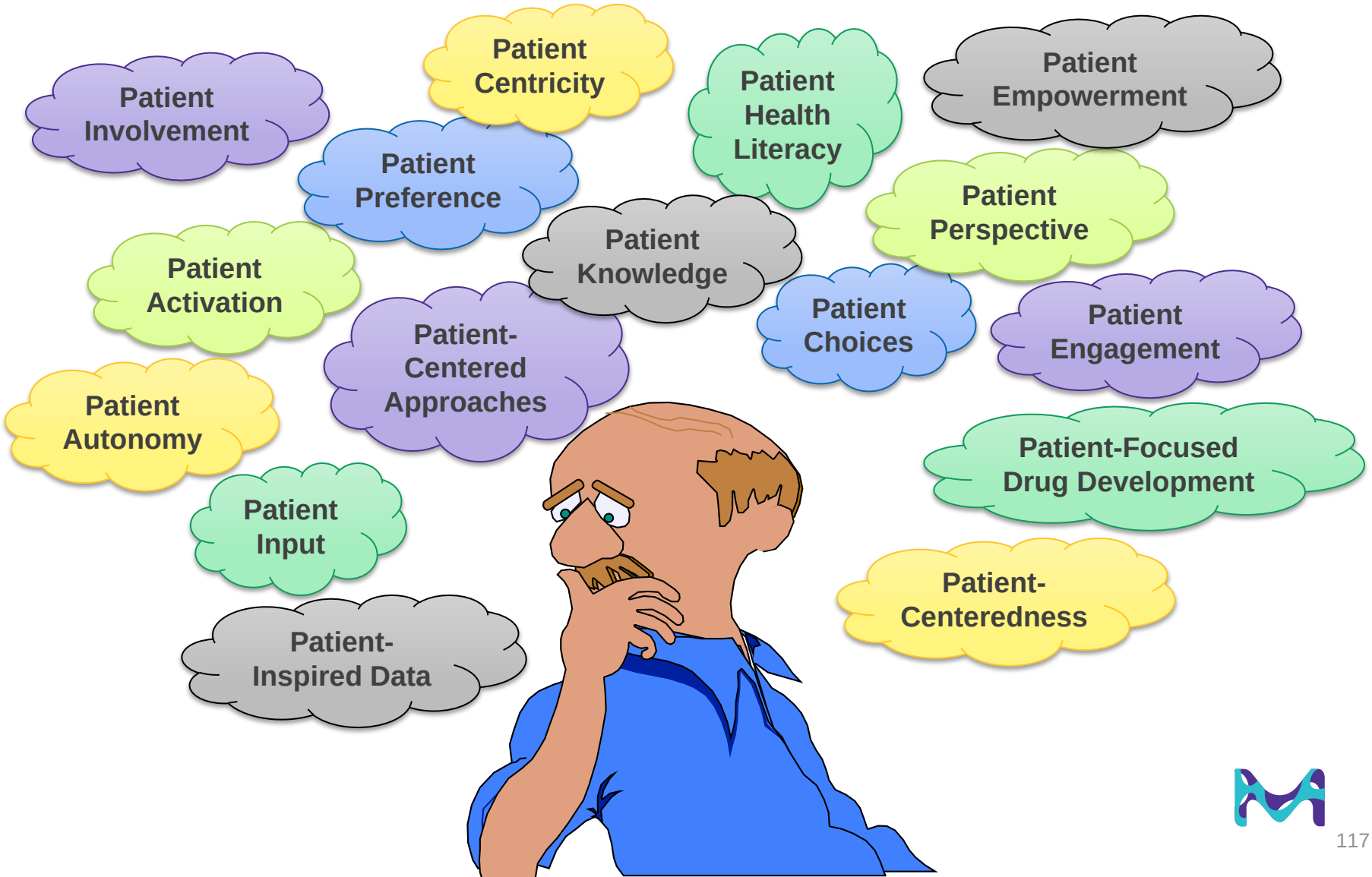
Methodological Issues to Resolve

- 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 (eg 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

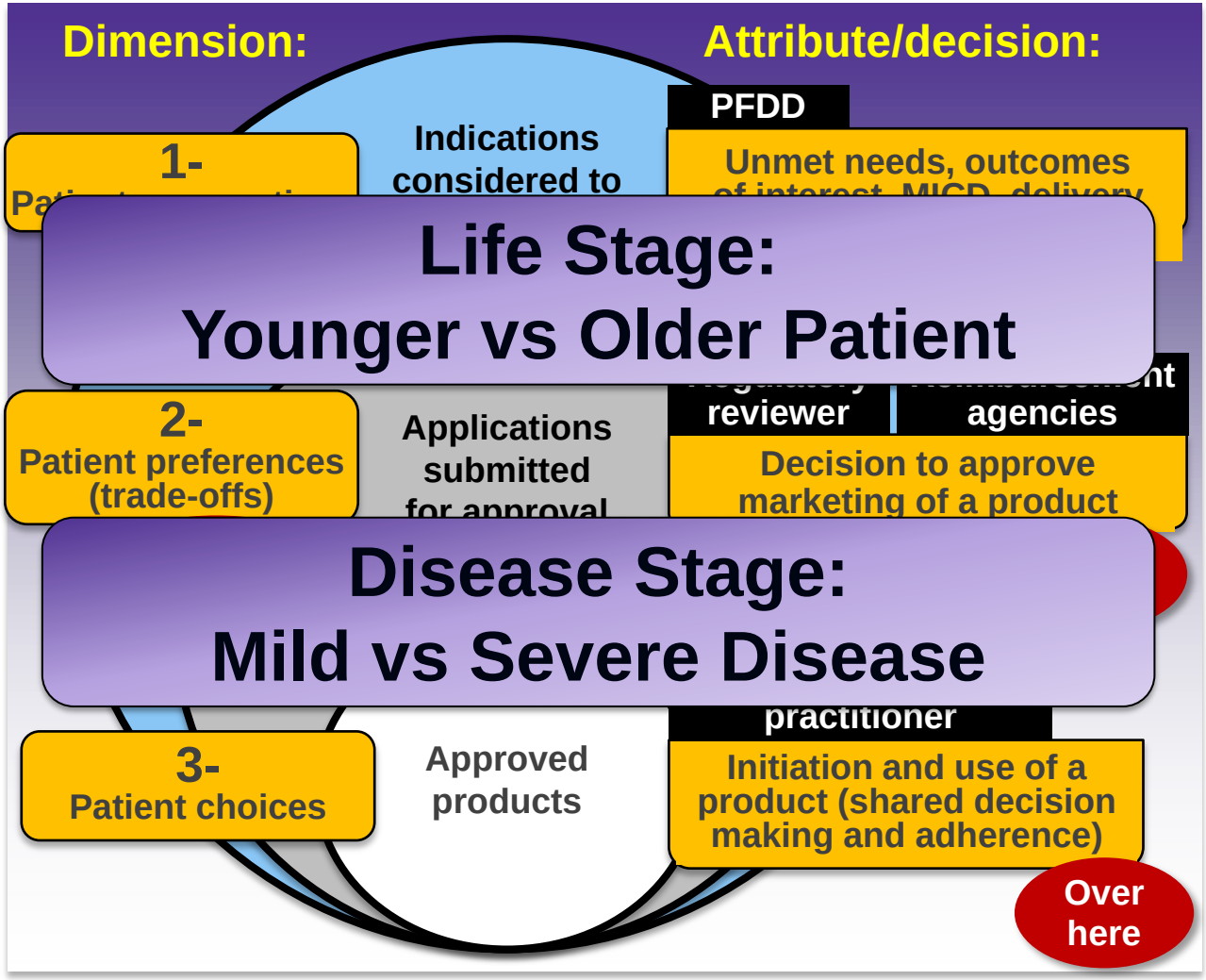
Outline

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

Need Vocabulary Control



Dimensions of Patient Engagement in Product Development: Perspectives vs Preferences vs Choices



What is missing?

A) Patient preference (trade-offs, benefits vs harms):

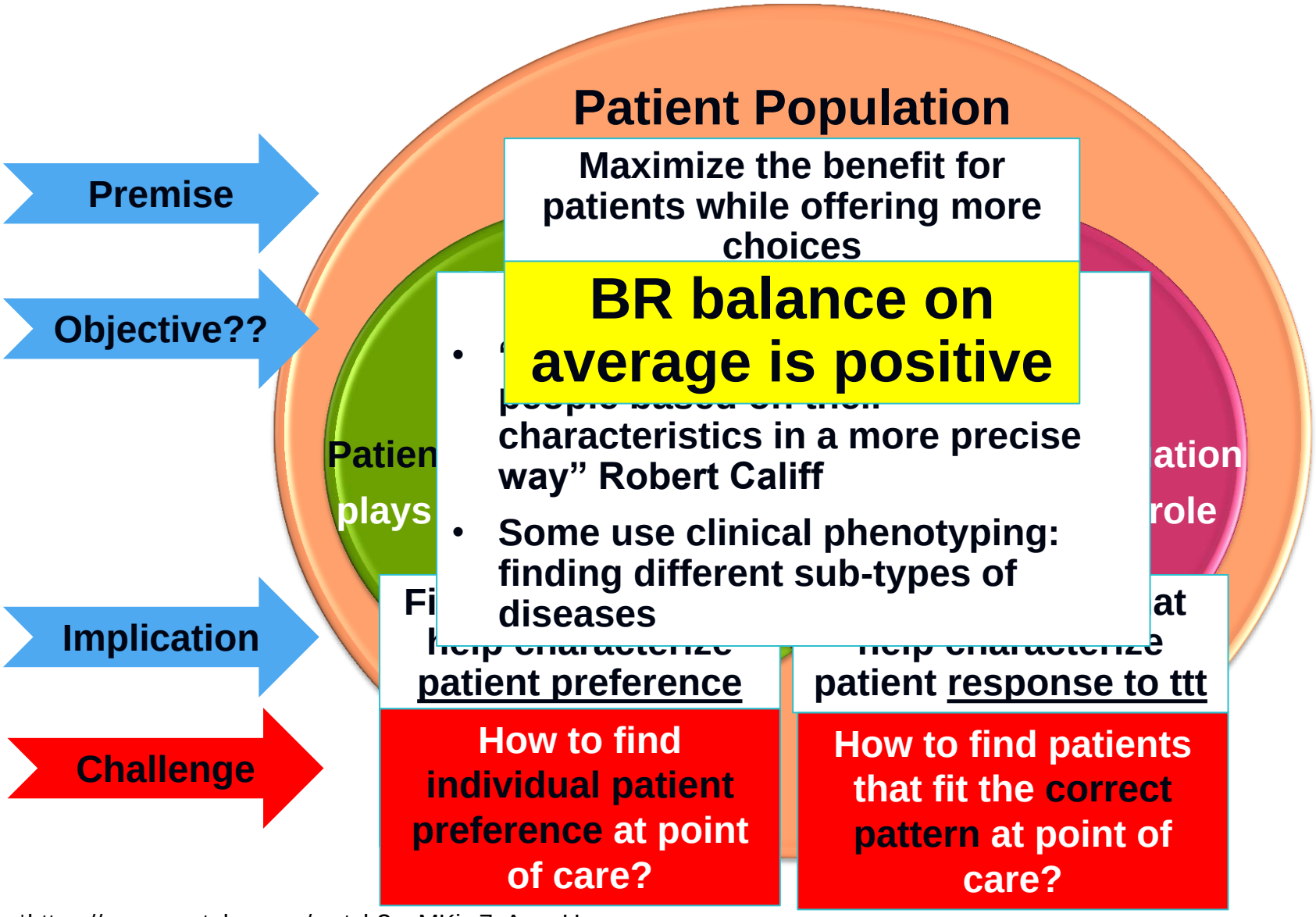
- Identify attributes of preference-sensitive scenarios
- Capture at pertinent disease and life milestones (who, what, when, and how)
- Integrate in the decision-making process at the time of approval, not after the fact (needs regulatory pathway)
- Anticipate in prospective patients

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

Hammad TA, Neyarapally GA (2016): Regulatory and Legislative Policy and Science Considerations in the Era of Patient-Centeredness, Big Data, and Value. In "Benefit-Risk Assessment Methods in Medicinal Product Development: Bridging Qualitative and Quantitative Assessments". CRC Press, Taylor & Francis Group.

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



*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

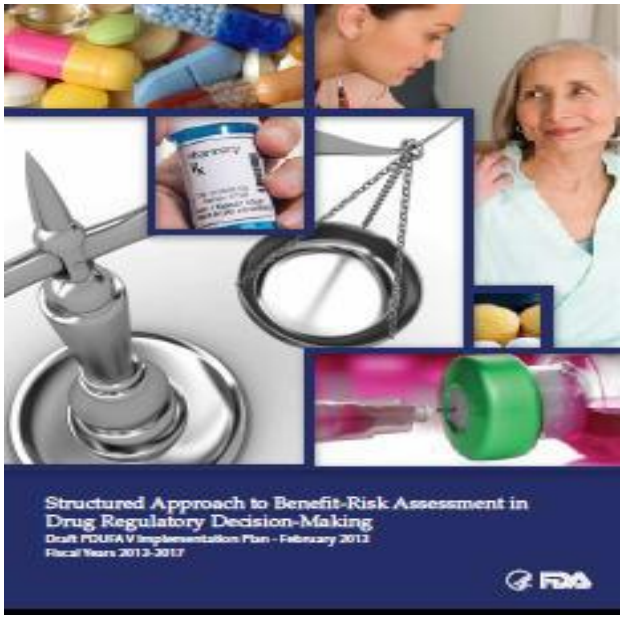
Disclaimer

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**



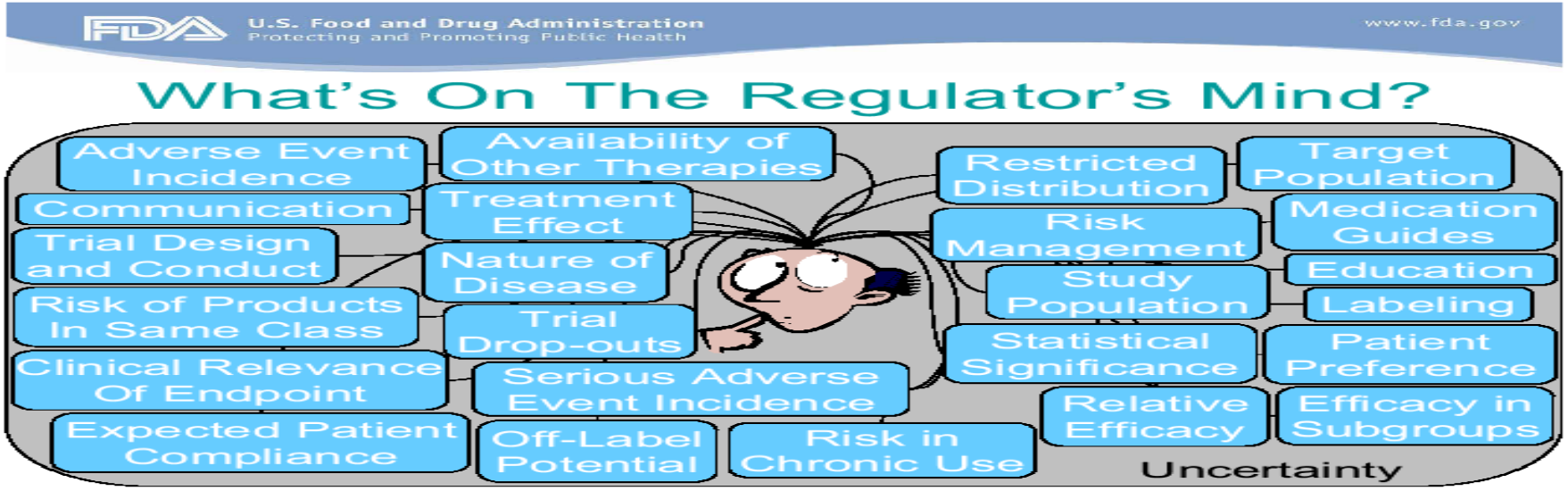
EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

pmda 独立行政法人 医薬品医療機器総合機構
Pharmaceuticals and Medical Devices Agency

So What Can Make Benefit-Risk Decision Making Challenging?

There are many factors that can make a decision challenging

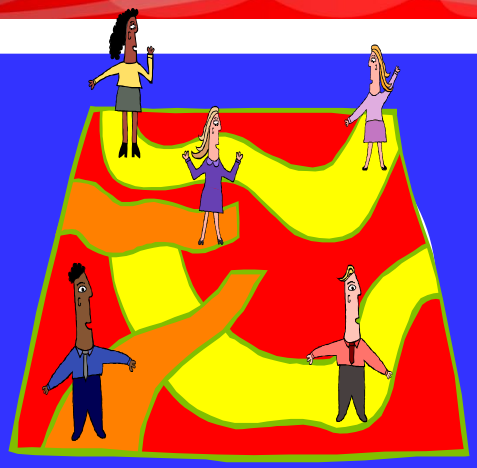
Lack of clarity	**Complexity**
Lack of certainty	**Conflicting objectives**
Lack of structure	**Inappropriate frame**
Lack of judgment criteria	**"What's on the Regulator's Mind"**



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

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

Decision Context

Benefit and Risk Attributes

Benefit-Risk Optimization

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

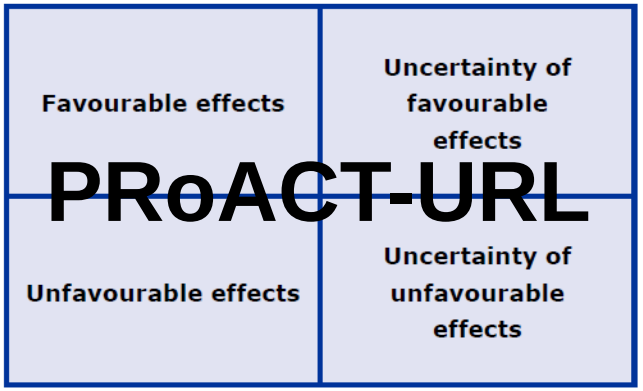
–Benefit-risk summary assessment

B-RA Frameworks: Support for Decision-Making and Communication

FDA

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

EMA



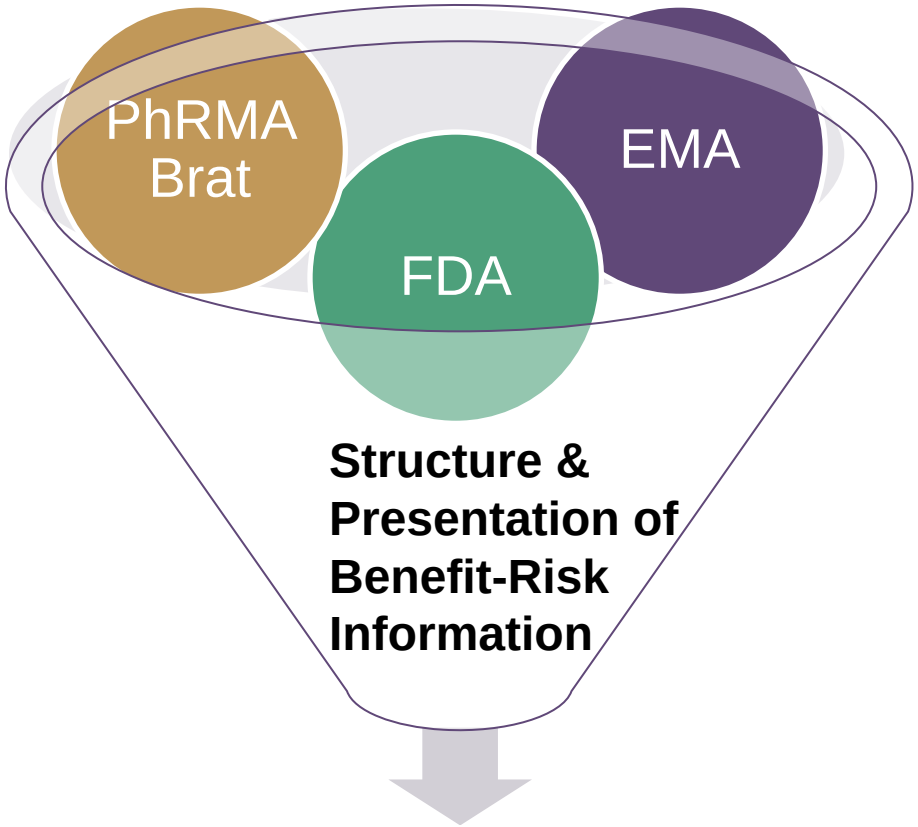
PhRMA BRAT

Table 1 Steps in applying the BRAT Framework

Step	Description
1. Define the decision context	Define drug, dose, formulation, indication, patient population, comparator(s), time horizon for outcomes, perspective of the decision makers (regulator, sponsor, patient, or physician)
2. Identify outcomes	Select all important outcomes and create the initial value tree. Define a preliminary set of outcome measures/end points for each. Document rationale for outcomes included/excluded
3. Identify and extract source data	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
4. Customize the framework	Modify the value tree on the basis of further review of the data and clinical expertise. Refine the outcome measures/ end points. May include tuning of outcomes not considered relevant to a particular benefit–risk assessment or that vary in relevance by stakeholder group
5. Assess outcome importance	Apply or assess any ranking or weighting of outcome importance to decision makers or other stakeholders
6. Display and interpret key benefit–risk metrics	Summarize source data in tabular and graphical displays to aid review and interpretation Challenge summary metrics, review source data, and identify and fill any information gaps Interpret summary information

BRAT = B-R action team; EMA = European Medicines Agency; FDA = Food and Drug Administration; PhRMA = Pharmaceutical Research and Manufacturers of America

So Which Framework?: Global Guidance Begins to Emerge

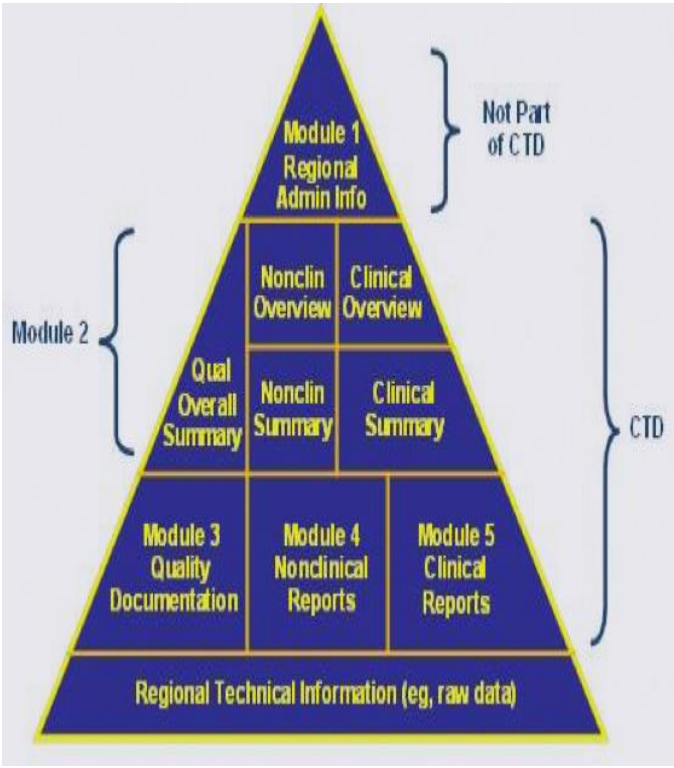


International Council on Harmonization (ICH): Revision of M4E Guideline Enhancing the Format and Structure of Benefit-Risk Information in ICH

The Clinical Overview

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

Capacity Building: Realizing PDUFA V&VI Benefit-Risk Goals (2)

- 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

Benefit-Risk & Related Work Streams

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

Current or 'Blue Sky' Activities

U.S. FOOD & DRUG ADMINISTRATION

Session 1

Panel Discussion and Q&A

Graham Thompson

Facilitator

September 18, 2017

U.S. FOOD & DRUG ADMINISTRATION

LUNCH

U.S. FOOD & DRUG ADMINISTRATION

Session 2

Approaches to Incorporating Patient Perspectives into Benefit-Risk Assessment

Pujita Vaidya
Facilitator

September 18, 2017

U.S. FOOD & DRUG ADMINISTRATION

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

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

Fiscal Year 2013	Fiscal Year 2014	Fiscal Year 2015	Fiscal Year 2016	Fiscal Year 2017
• Chronic fatigue syndrome/ myalgic encephalomyelitis • HIV • Lung cancer • Narcolepsy	• Sickle cell disease • Fibromyalgia • Pulmonary arterial hypertension • Inborn errors of metabolism • Hemophilia A, B, and other heritable bleeding disorders • Idiopathic pulmonary fibrosis	• Female sexual dysfunction • Breast cancer • Chagas disease • Functional gastrointestinal disorders • Huntington's disease and Parkinson's disease • Alpha-1 antitrypsin deficiency	• Non-tuberculous mycobacterial lung infections • Psoriasis • Neuropathic pain associated with peripheral neuropathy • Patients who have received an organ transplant	• Sarcopenia • Autism • Alopecia areata • Hereditary angioedema (September 25)

Participation Estimates

In-Person	Registered	Attended
Patient / Representatives	40 – 185	30 - 120
Other (e.g., NIH, industry)	40 – 115	30 - 140
Webcast	250 - 650	~50% of registered
Docket Submissions	5 - 400	

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 of areas of unmet need
  - Develop clinical outcome tools (PROs, etc.) that better address patient needs

150

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

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

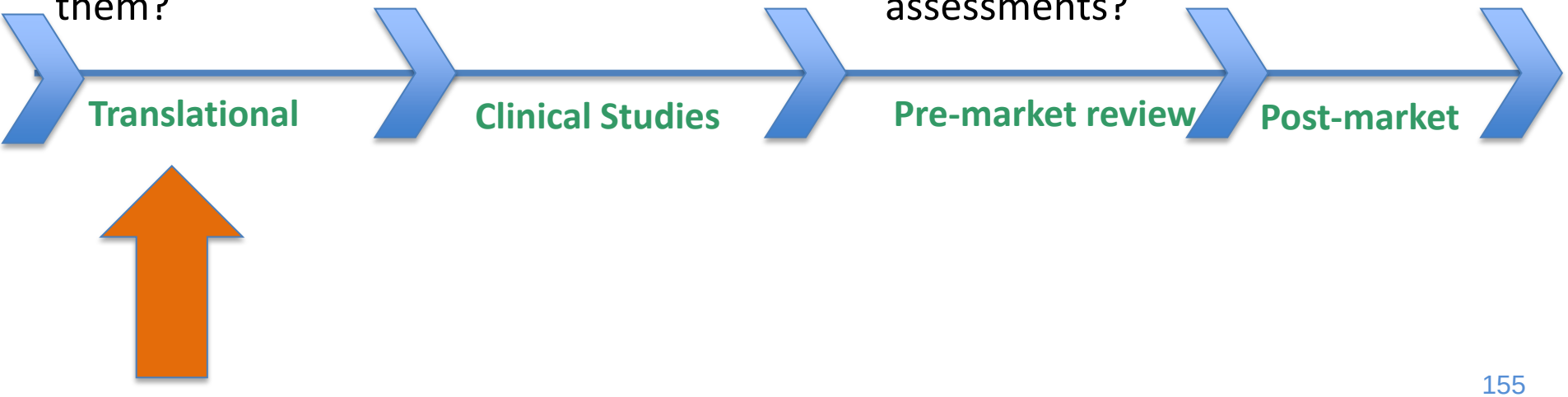
Further integrating patient perspective into drug development and decision making

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?

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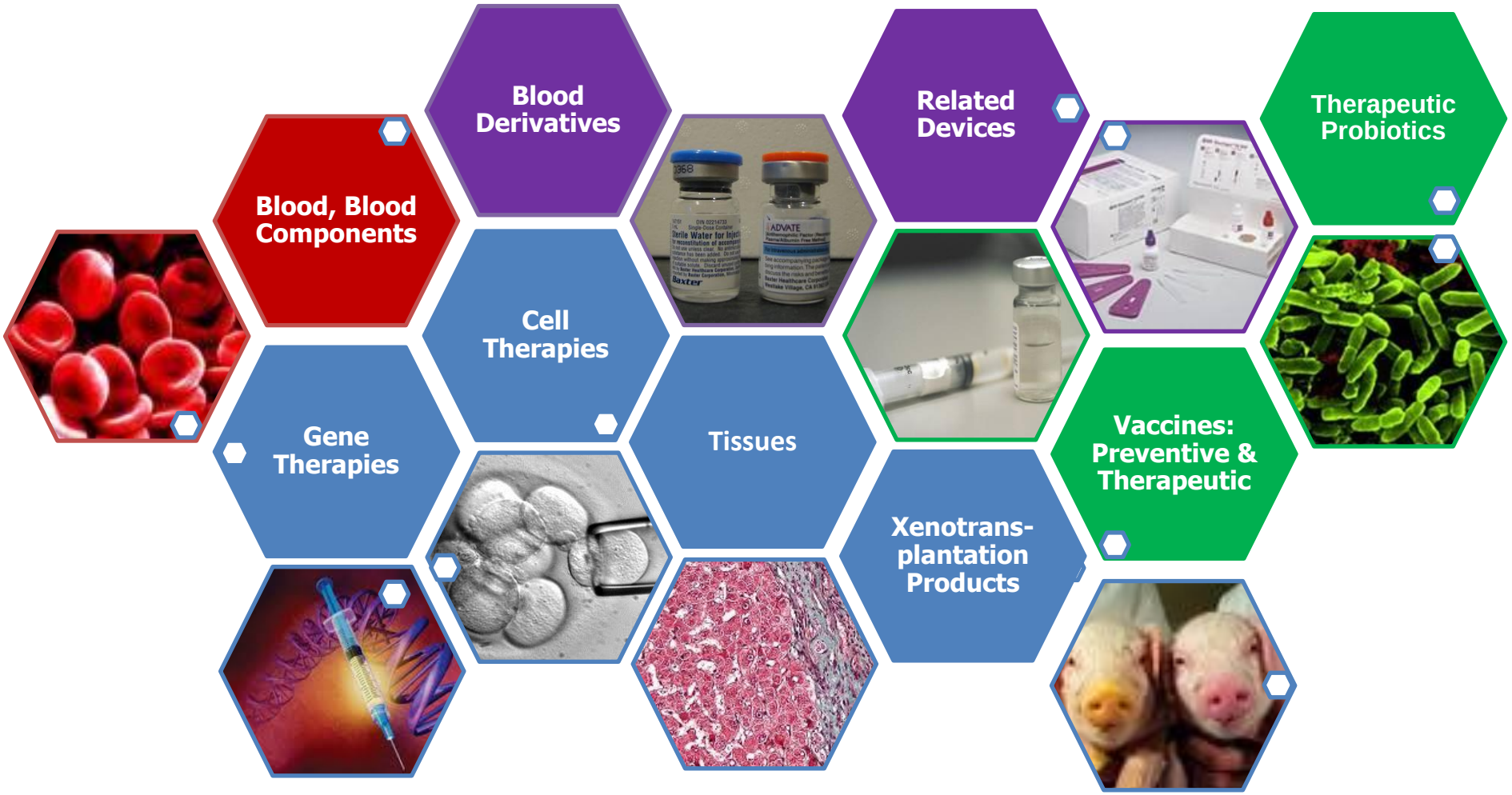
Incorporating Patient Preferences into Regulatory Benefit-Risk Assessment

Telba Irony, PhD
Deputy Director

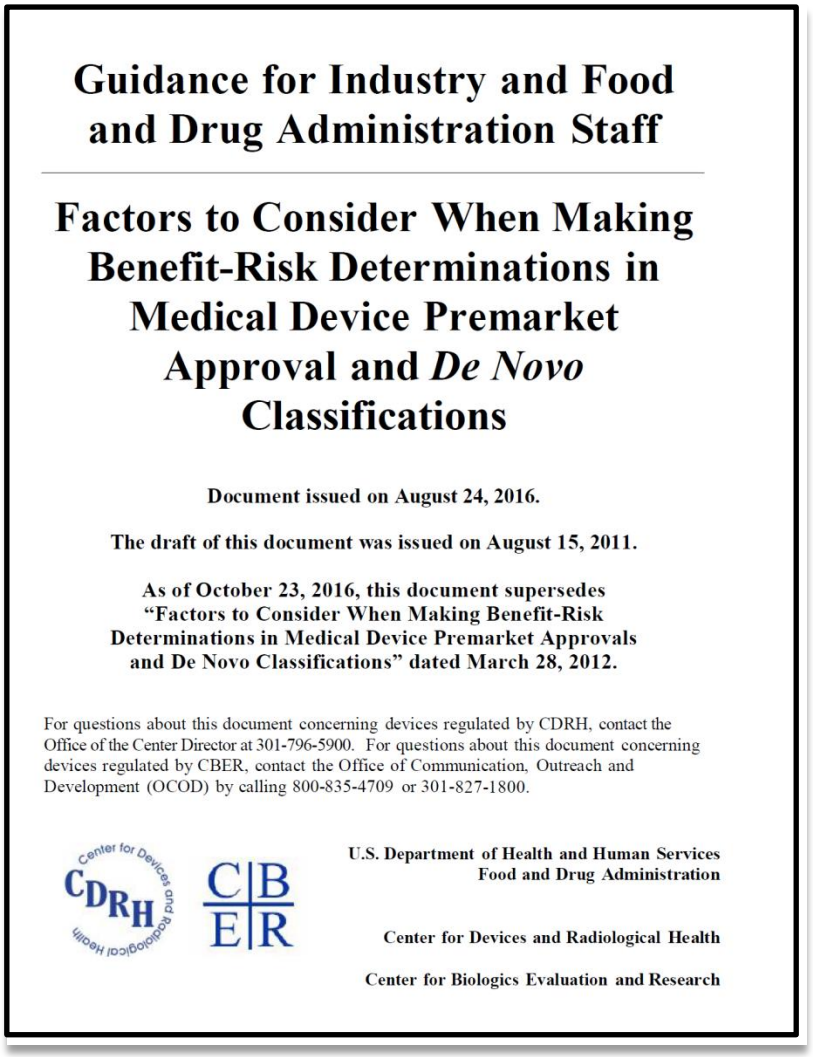
Office of Biostatistics and Epidemiology
Center for Biologics Evaluation and Research
FDA - CBER

September 18, 2017

What does CBER regulate?



Factors for Benefit – Risk Determinations (2016) Center for Devices and Center for Biologics



Guidance for Industry and Food and Drug Administration Staff

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U.S. Department of Health and Human Services
Food and Drug Administration

Center for Devices and Radiological Health

Center for Biologics 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

Factor
Patient tolerance for risk & perspective on benefit

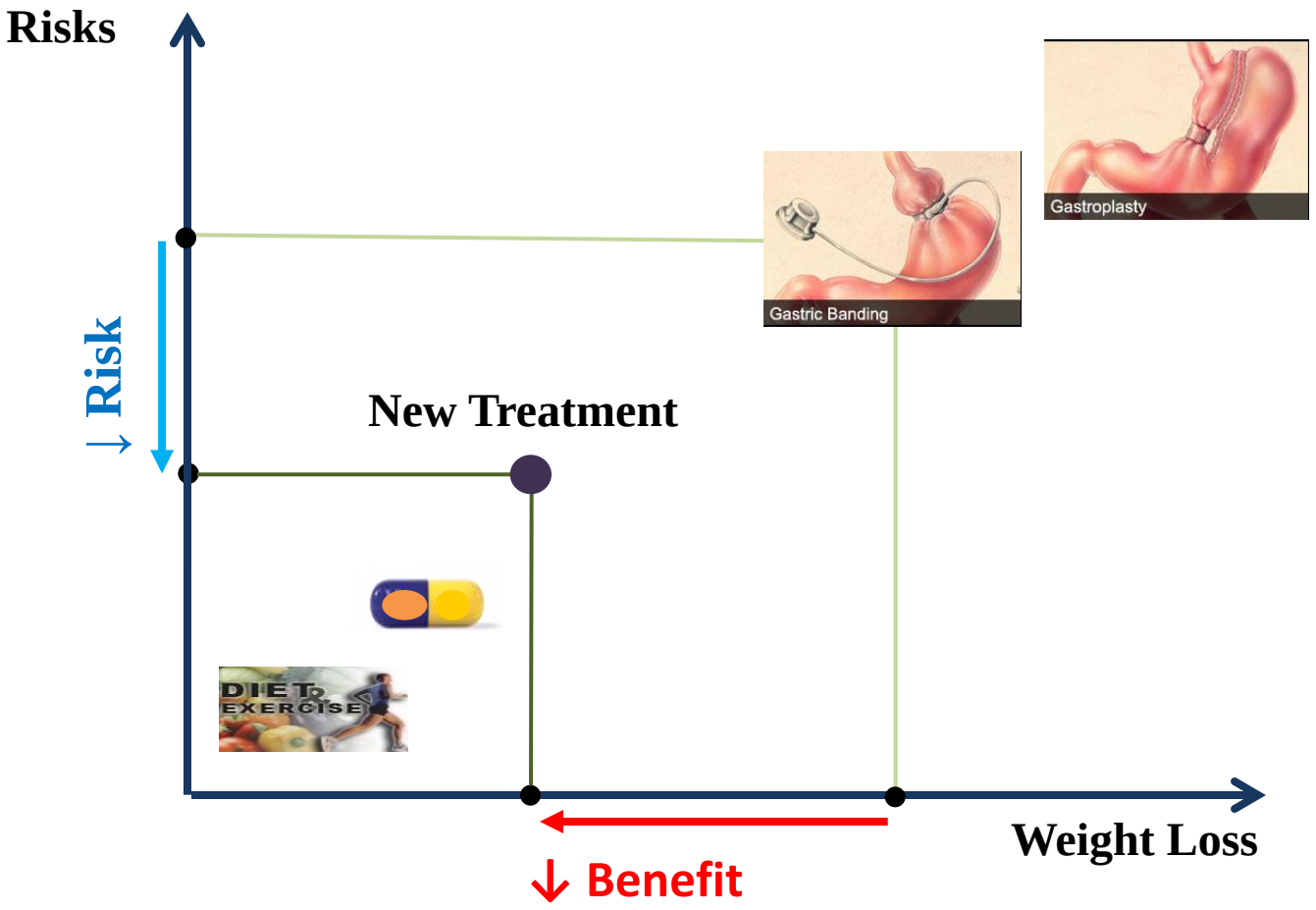
"Risk tolerance will vary among patients, and this will affect individual patient decisions as to whether the risks are acceptable in exchange for a probable benefit. ***… FDA would consider evidence relating to patients' perspective of what constitutes a meaningful benefit."***

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?



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

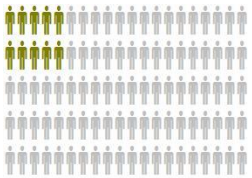
Attributes and Levels: Obesity Study

Attribute	Levels
Type of Operation	Endoscopic Laparoscopic Open Surgery
Diet restrictions	Eat ¼ cup at a time Wait 4 hours between eating Can't eat hard-to-digest foods
Average weight-loss	5% of body weight 10% of body weight 20% of body weight 30% of body weight
How long weight-loss lasts	6 months 1 year 5 years
Comorbidity improvement	None Reduce risk (or current dosage) by half Eliminate risk (or current dosage)

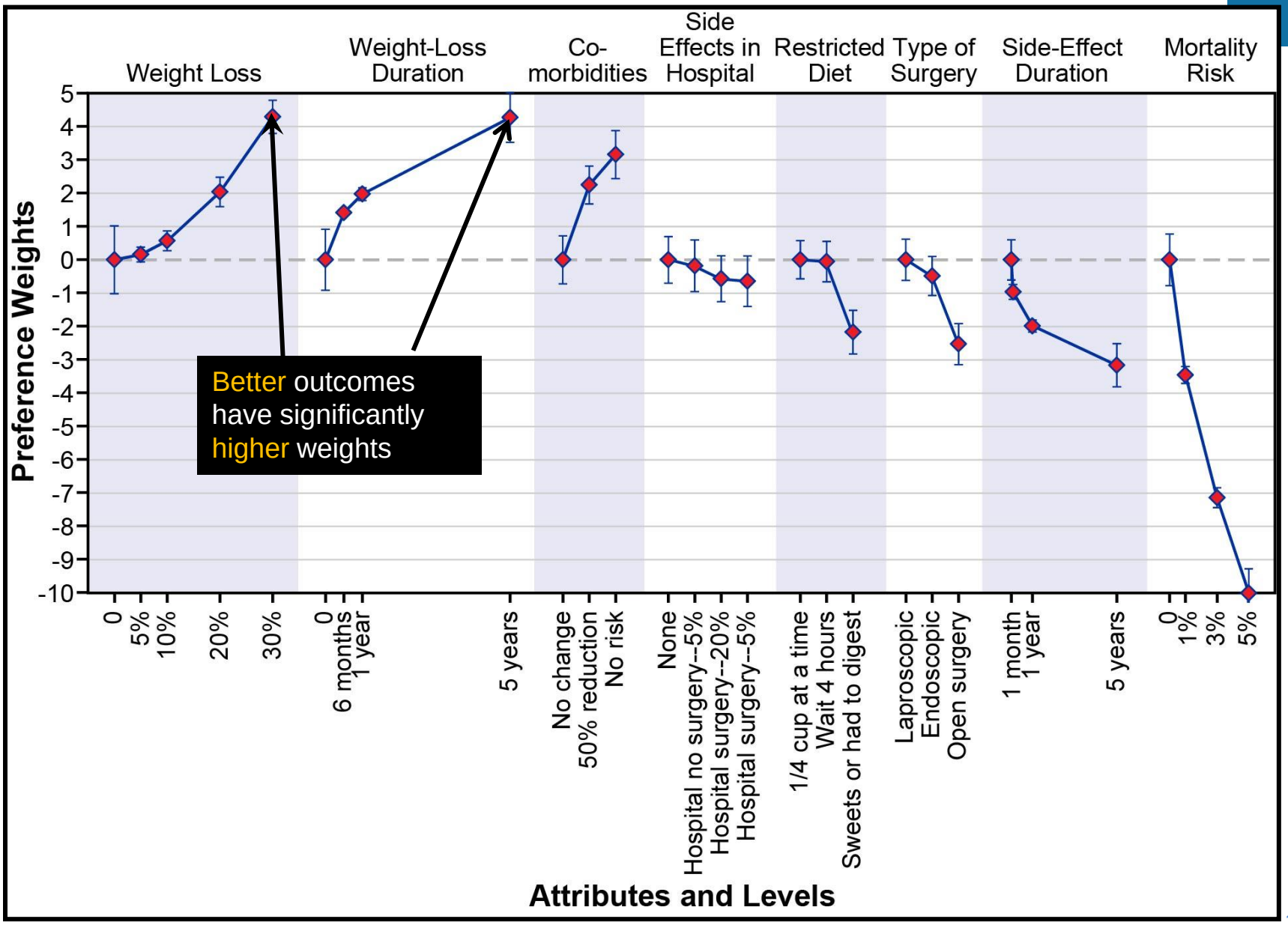
Attributes and Levels: Obesity Study

Attribute	Levels
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%

Choice Question Example

Feature	Device A	Device B
Type of operation	Endoscopic surgery	
Recommended diet restriction	Wait 4 hours between meals	
On average, how much weight is lost	30 lbs.	60 lbs.
On average, how long the weight loss lasts	Weight loss lasts 5 years	Weight loss lasts 1 year
Average reduction in dose of prescription drugs for diabetes at the lower weight	Eliminates the need for prescription drug	
On average, how long side effects last (Remember that side effects will limit your ability to do daily activities several times a month.)	Last 1 month	Last 1 year
Chance of a side effect requiring hospitalization	None	
Chance of dying from getting the weight loss device	 **10%** **(10 out of 100)**	 **1%** **(1 out of 100)**
Which weight-loss device do you think is better for people like you?	 Device A	 Device B

Results: Preference Weights



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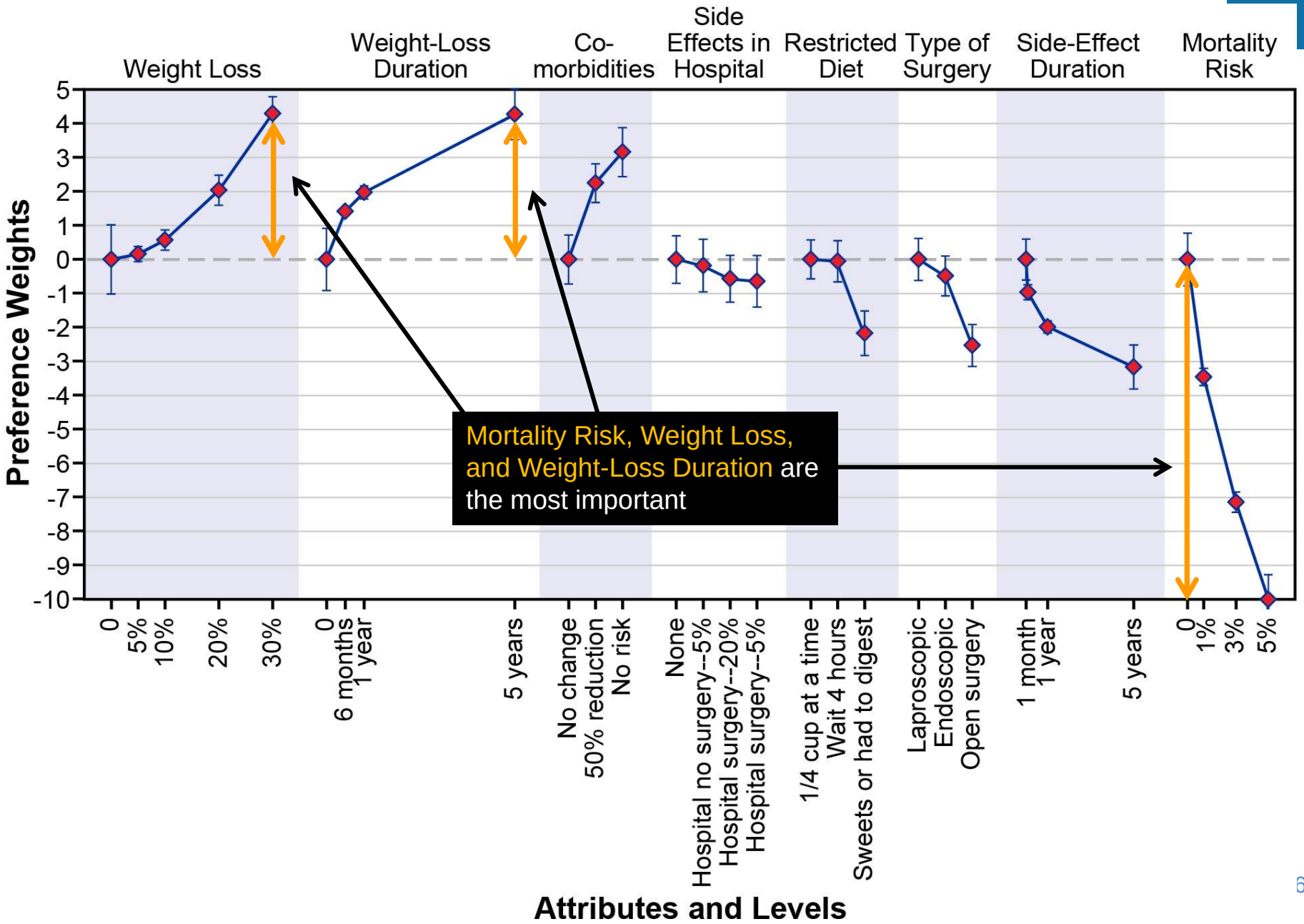


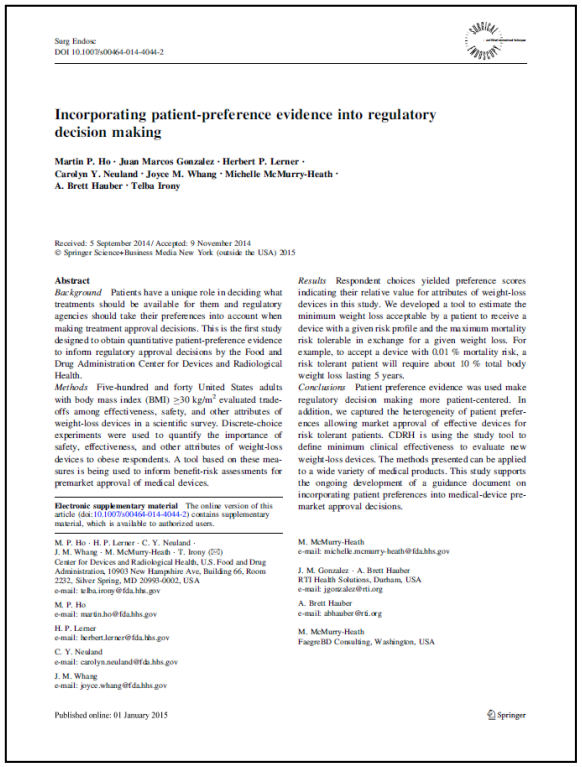
Decision Aid Tool

- 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



Surg Endosc
DOI 10.1007/s00464-014-4044-2

Incorporating patient-preference evidence into regulatory decision making

Martin P. Ho · Juan Marcos Gonzalez · Herbert P. Lerner · Carolyn Y. Neuland · Joyce M. Whang · Michelle McMurry-Heath · A. Brett Hauber · Telba Irony

Received: 5 September 2014 / Accepted: 9 November 2014

Abstract
Background Patients have a unique role in deciding what treatments should be available for them and regulatory agencies should take their preferences into account when making treatment approval decisions. This is the first study designed to obtain quantitative patient-preference evidence to inform regulatory approval decisions by the Food and Drug Administration Center for Devices and Radiological Health.
Methods Five-hundred and forty United States adults with body mass index (BMI) ≥30 kg/m^2 evaluated trade-offs among effectiveness, safety, and other attributes of weight-loss devices in a scientific survey. Discrete-choice experiments were used to quantify the importance of safety, effectiveness, and other attributes of weight-loss devices to obese respondents. A tool based on these measures is being used to inform benefit-risk assessments for premarket approval of medical devices.
Results Respondent choices yielded preference scores indicating their relative value for attributes of weight-loss devices in this study. We developed a tool to estimate the minimum weight loss acceptable by a patient to receive a device with a given risk profile and the maximum mortality risk tolerable in exchange for a given weight loss. For example, to accept a device with 0.01 % mortality risk, a risk tolerant patient will require about 10 % total body weight loss lasting 5 years.
Conclusions Patient preference evidence was used make regulatory decision making more patient-centered. In addition, we captured the heterogeneity of patient preferences allowing market approval of effective devices for risk tolerant patients. CDRH is using the study tool to define minimum clinical effectiveness to evaluate new weight-loss devices. The methods presented can be applied to a wide variety of medical products. This study supports the ongoing development of a guidance document on incorporating patient preferences into medical-device premarket approval decisions.

Electronic supplementary material The online version of this article (doi:10.1007/s00464-014-4044-2) contains supplementary material, which is available to authorized users.

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Published online: 01 January 2015

Springer

Patient Preference Information – Voluntary Submission, Review in Premarket Approval Applications, Humanitarian Device Exemption Applications, and *De Novo* Requests, and Inclusion in Decision Summaries and Device Labeling

Guidance for Industry, Food and Drug Administration Staff, and Other Stakeholders

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For questions about this document regarding CDRH-regulated devices, contact the Office of the Center Director (CDRH) at 301-796-5900 or Anindita Saha at 301-796-2537 (Anindita.Saha@fda.hhs.gov)..

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U.S. Department of Health and Human Services
Food and Drug Administration

Center for Devices and Radiological Health

Center for Biologics Evaluation and Research

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

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

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**


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Using Patient Input in Regulatory Decision Making at CDRH

Martin Ho, MS

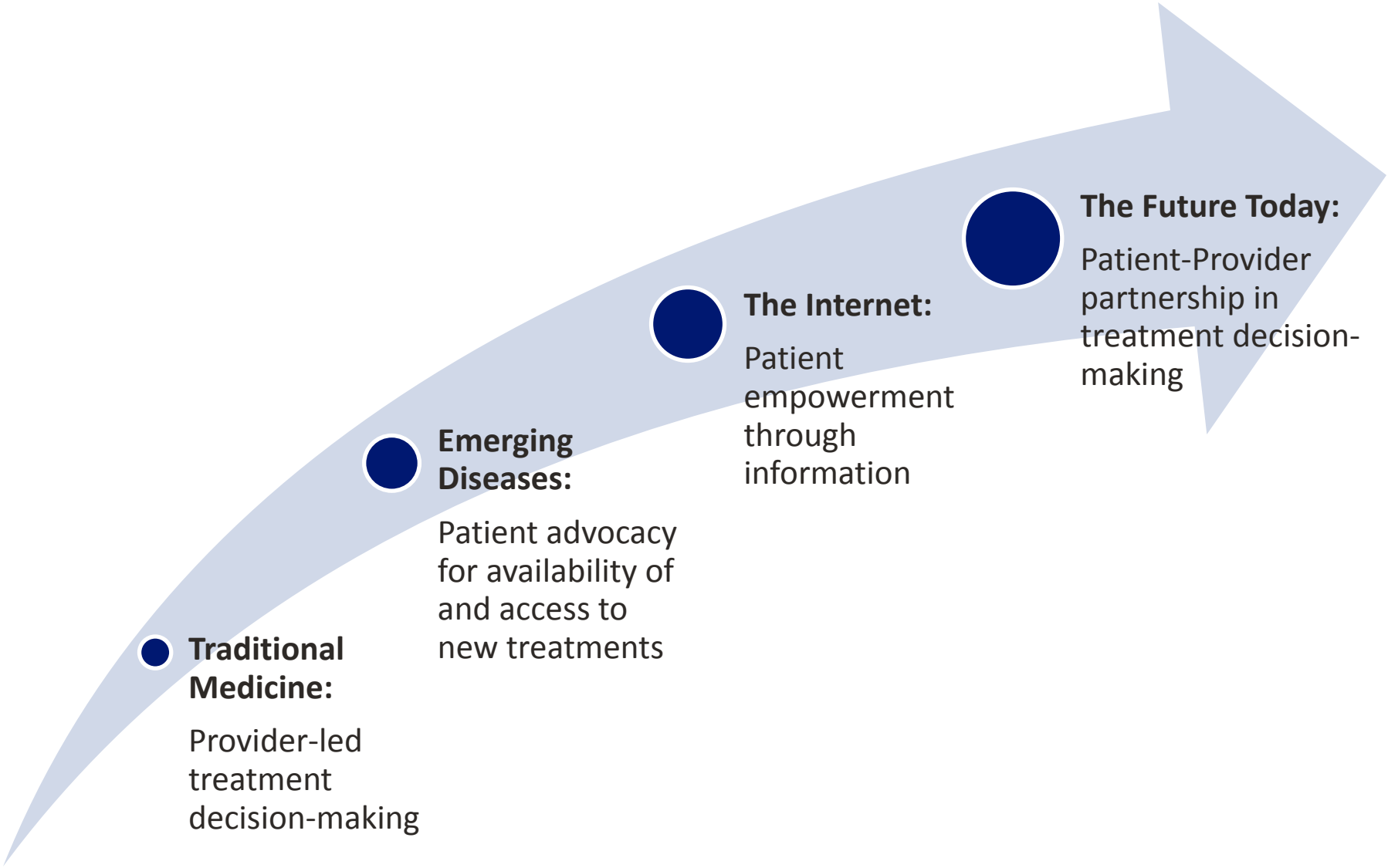
Associate Director for Quantitative Innovations
Office of the Surveillance and Biometrics
Center for Devices and Radiological Health

September 18, 2017

Patients are at the Heart of What We Do

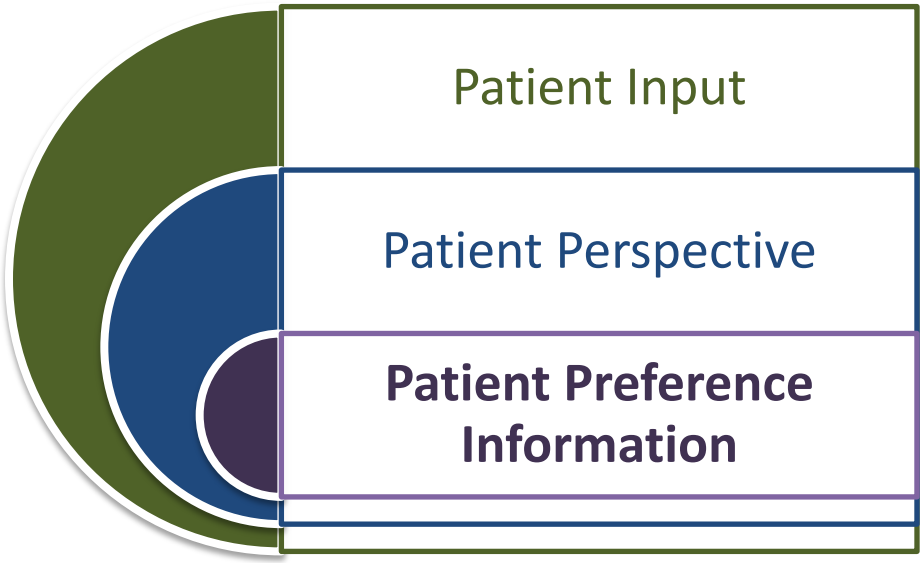
CDRH Vision: Patients in the U.S. have access to high-quality, safe, and effective medical devices of public health importance first in the world

Evolution of the Role of the Patient



Patient Input

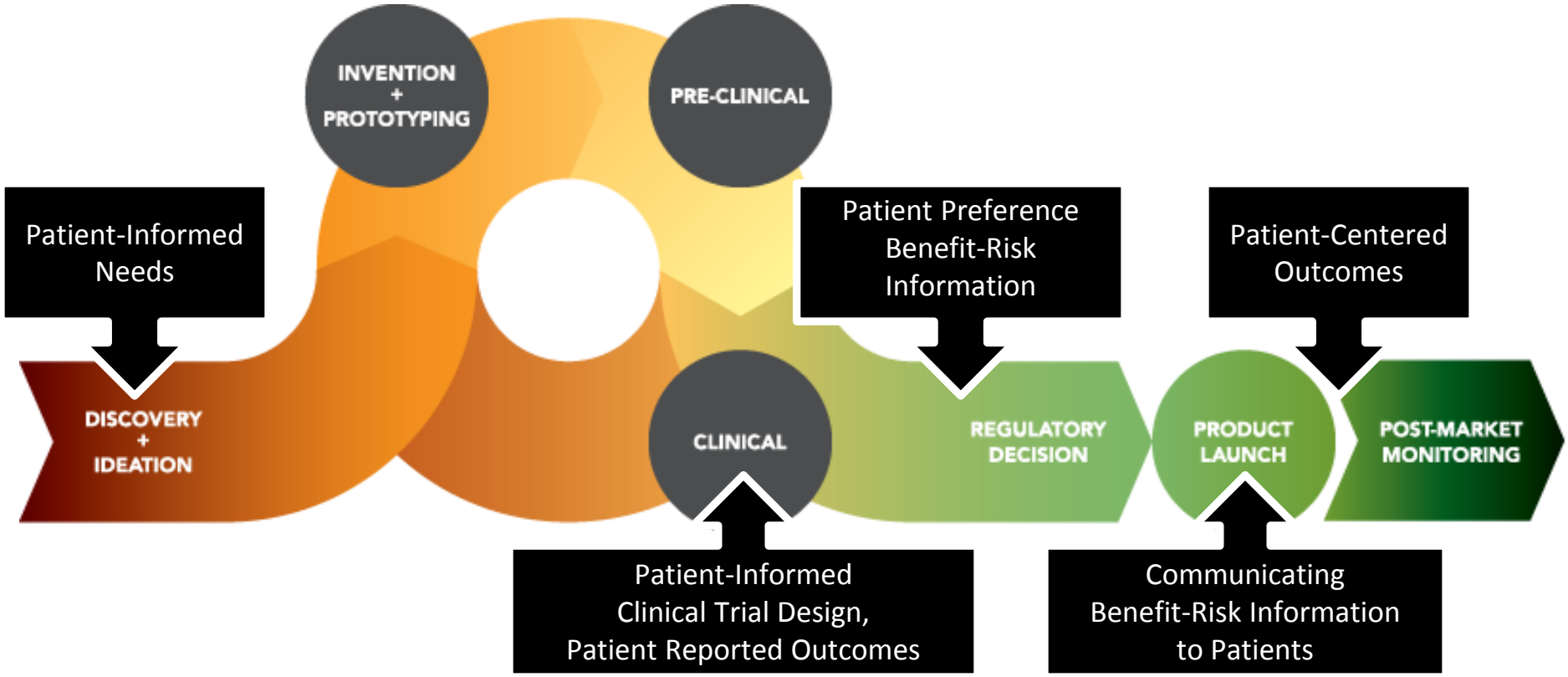
- Patient input includes a wide range of information and perspectives
  - Anecdotal comments in correspondence to the FDA
  - Testimony at Advisory Committee Panel meetings
  - Patient opinions expressed publicly including through social media
  - Patient responses to qualitative *ad hoc* surveys
  -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



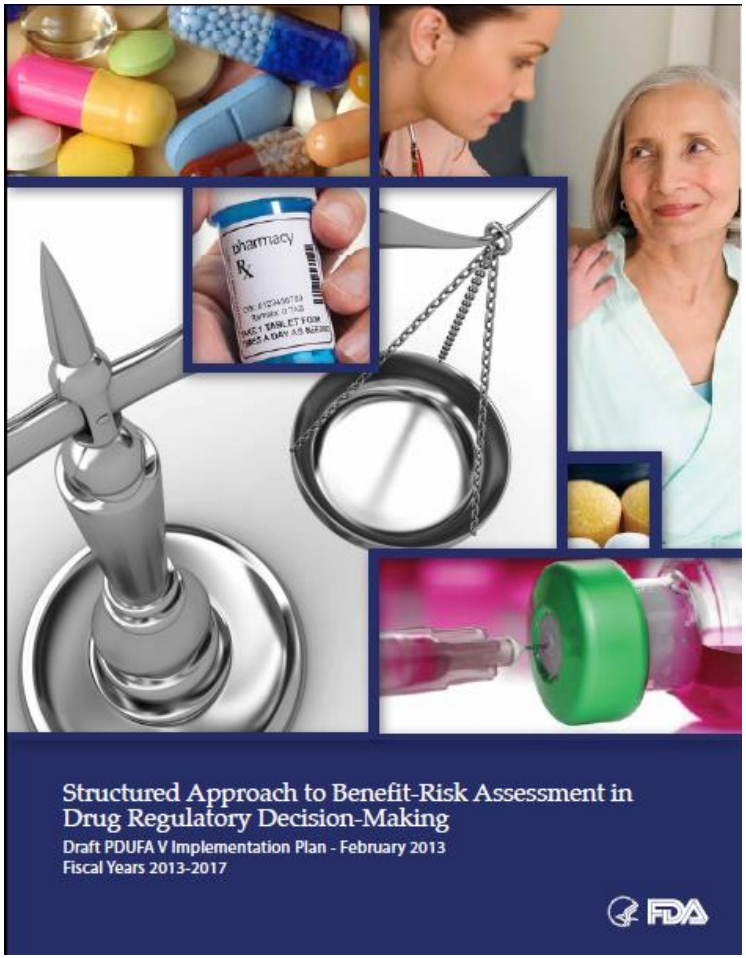
Patient Perspectives

- 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

Regulatory Impact



FDA Benefit-Risk Frameworks



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CDRH Guidance on Factors to Consider for Benefit – Risk Determinations (2016)

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

PPI Factors	Questions
Patient-Reported Outcomes	• Do benefit(s) and risk(s) include effects on patients' health-related quality of life?
Benefit-Risk Considerations	• Which benefits and risks are most important to affected patients? • What benefit-risk tradeoffs are acceptable from the patient perspective? • Are there clinically-relevant subgroups of patients that would choose a particular benefit-risk profile over other alternatives? • Does PPI capture diverse preference across the spectrum of indicated population and thus, generalizable?

CDRH Strategic Priority 2016 – 2017
Partner with Patients

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

https://www.federalregister.gov/documents/2017/07/26/2017-15657/patient-engagement-advisory-committee-notice-of-meeting

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


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RTI (h)(s)
Health Solutions

18 September 2017

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

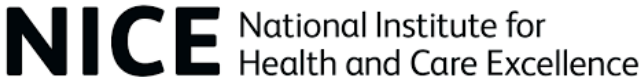
Brett Hauber, PhD

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

Introduction

- 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

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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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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."'

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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"

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

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“‘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”

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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.

whether the drug was providing any benefit.”’

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

for things”’

***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

Attributes	**What Matters**	Can often be obtained using qualitative methods
		Simple quantitative methods can be used to separate those attributes that matter to patients from those attributes that do not

Three Types of Patient Preference Information

Attributes	**What Matters**	Can often be obtained using qualitative methods
		Simple quantitative methods can be used to separate those attributes that matter to patients from those attributes that do not
Relative importance	**How much it matters**	Requires using quantitative methods that provide a weight for each attribute

Three Types of Patient Preference Information

Attributes	**What Matters**	Can often be obtained using qualitative methods
		Simple quantitative methods can be used to separate those attributes that matter to patients from those attributes that do not
Relative importance	**How much it matters**	Requires using quantitative methods that provide a weight for each attribute
Tradeoffs	**How much it matters and what tradeoffs are patients willing to make**	Patients are willing to make to obtain or avoid a given attribute.
		Can be approximated by comparing the weights that patients assign to each attribute
		Obtaining accurate trade-off information may require quantitative methods designed explicitly for this

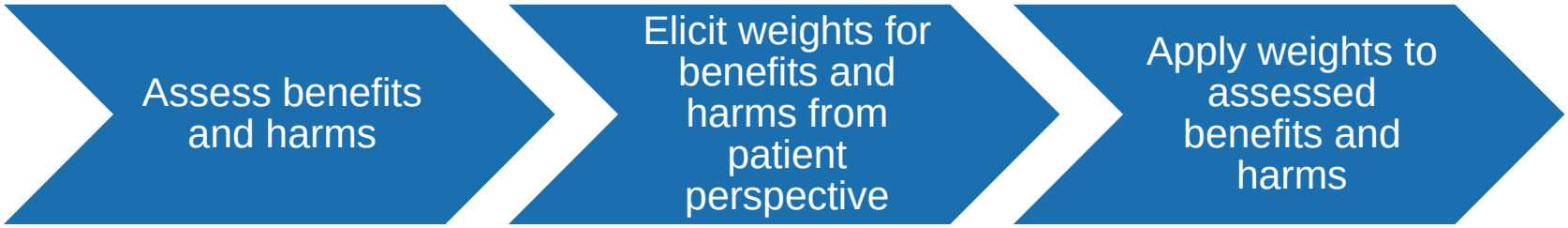
Three Types of Patient Preference Information

RTI (h)(s) Health Solutions

Attributes	**Wha ers**	Can often be obtained using qualitative methods
		Simple quantitative methods can be used to separate those attributes that matter to patients from those attributes that do not
Relative importance	**How h it matt**	Requires using quantitative methods that provide a weight for each attribute
Tradeoffs	**How h it ma d what deoffs are patients willing to make**	Patients are willing to make to obtain or avoid a given attribute.
		Can be approximated by comparing the weights that patients assign to each attribute
		Obtaining accurate trade-off information may require quantitative methods designed explicitly for this

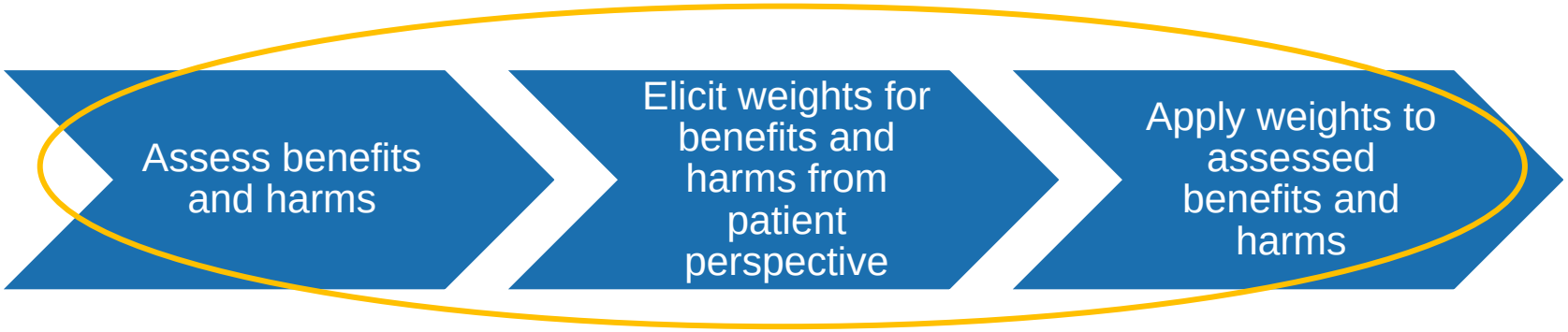
Three Approaches to Incorporating Patient Preferences in Benefit-Risk Assessment

Benefit-Risk Assessment



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

Benefit-Risk Preference Assessment: Approach 1



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

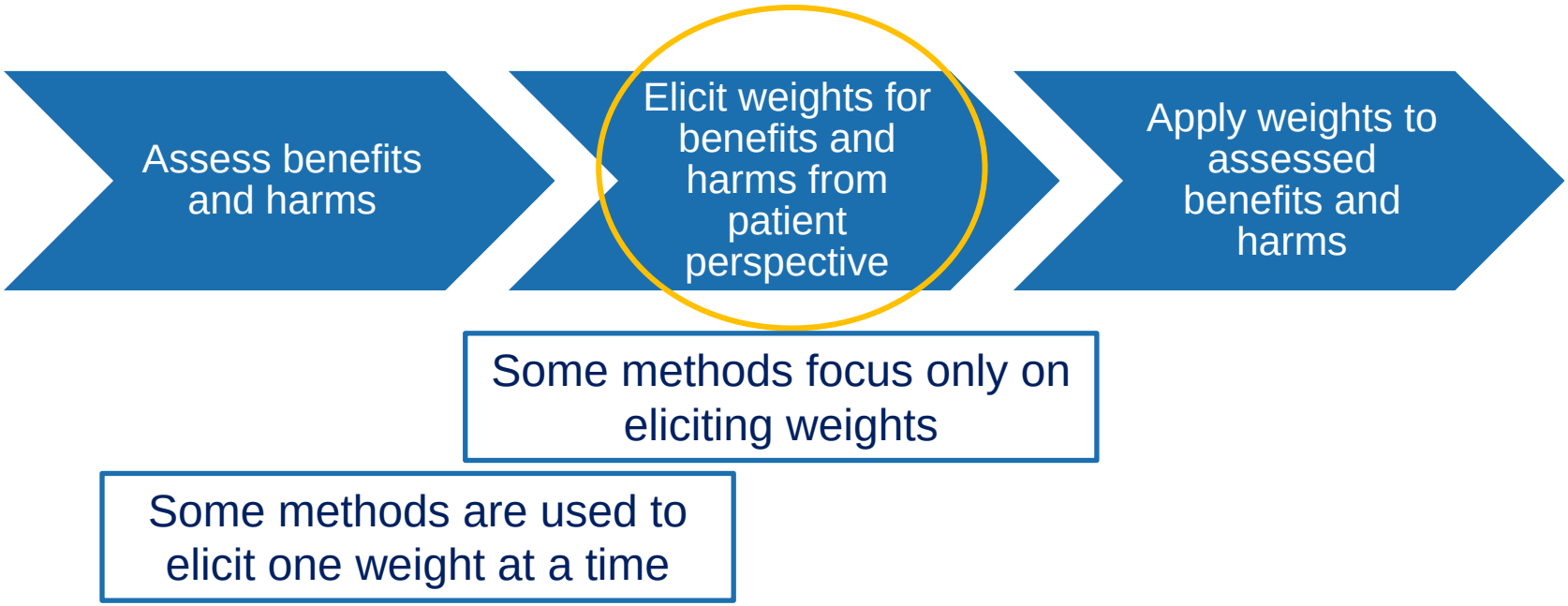
Postmus et al., Clinical Pharmacology & Therapeutics, 2016

Benefit-Risk Preference Assessment: Approach 2

Some methods focus only on eliciting weights

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

Benefit-Risk Preference Assessment; Approach 2a



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

Example: Parkinson's Device Preference Study

RTI (h)(s) Health Solutions

1 Identify the outcomes important to patients, family members, and caregivers

FDA

THE MICHAEL J. FOX FOUNDATION FOR PARKINSON'S RESEARCH

2 Design and conduct a patient preference assessment study

RTI (h)(s) Health Solutions

THE MICHAEL J. FOX FOUNDATION FOR PARKINSON'S RESEARCH

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

Align › Achieve › Accelerate

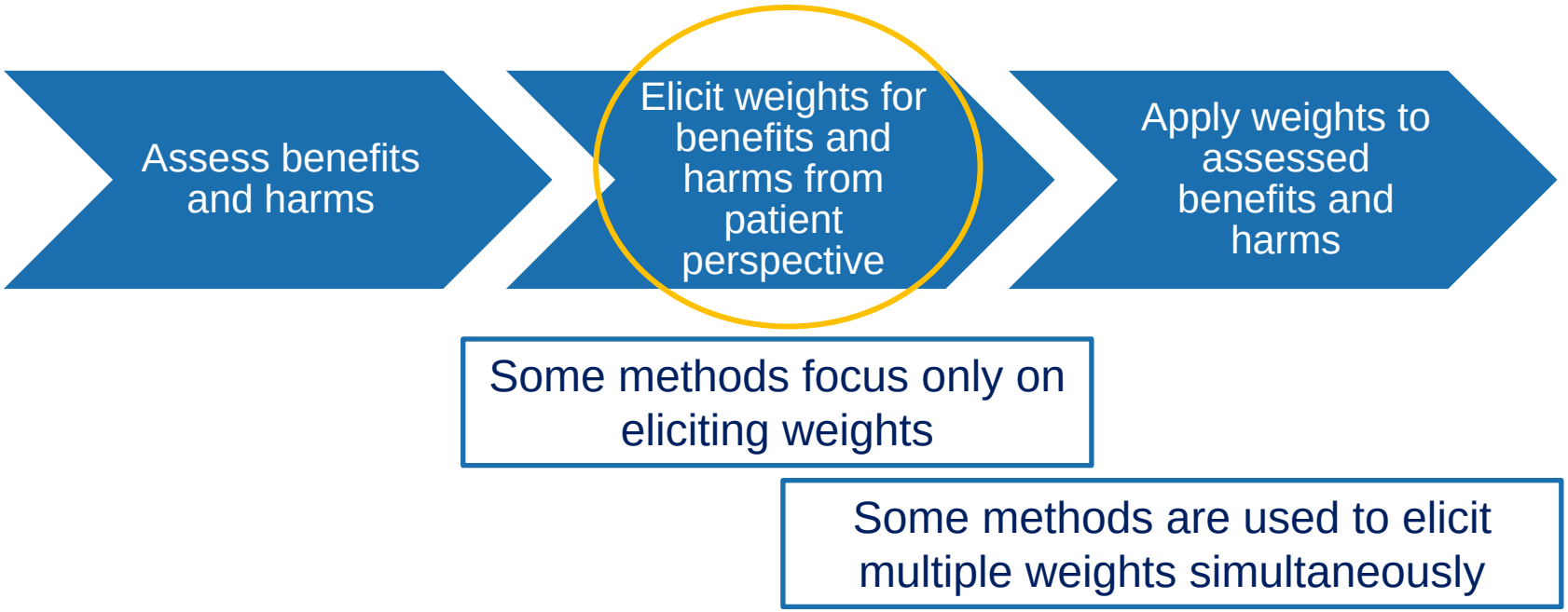
Example: Parkinson's Device Preference Study

RTI (h)(s) Health Solutions

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

Benefits	Burdens
Increase in daily "on time" (50% decrease in "off time")	Risk of (worsening) depression or anxiety
50% decrease in motor symptoms	Risk of serious adverse event (brain bleed)
50% decrease in PD pain	Increase in 1-year mortality risk
50% decrease in cognitive impairment	
50% in medication and side effect burden	

Benefit-Risk Preference Assessment: Approach 2b



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

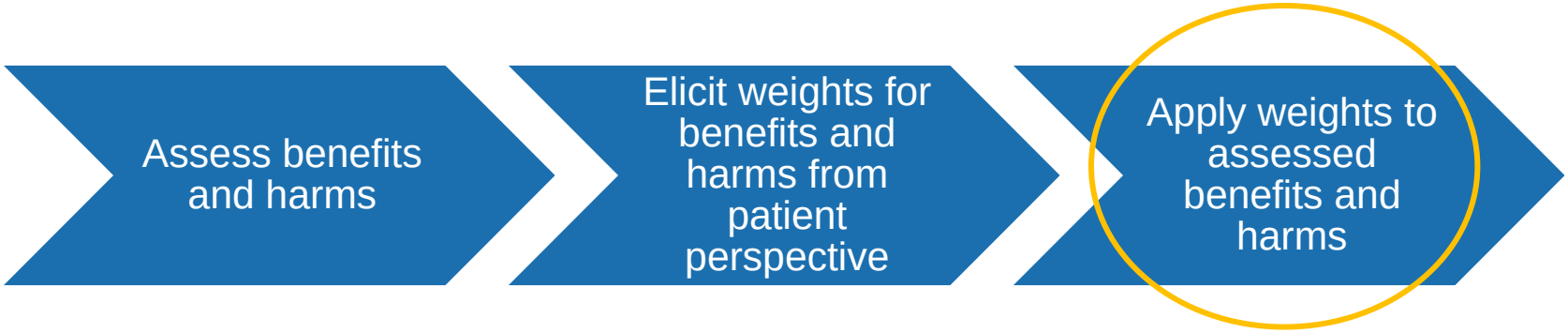
VBLOC Maestro® Rechargeable System

- 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



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

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

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

Source: MDIC PCBR Framework Report Release Event, May 13, 2015.
Available at: http://mdic.org/pcbr-framework-report-release/

Key Messages

If you only remember a few things about this presentation

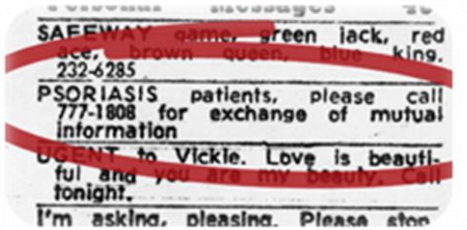
- ✓ Before we can measure how much something matters, shouldn't we first determine what matters?
- ✓ Preferences can provide systematic, quantitative evidence of stakeholder perspectives on the relative weights of benefits and risks
- ✓ There are precedents for doing this
- ✓ There are multiple approaches 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

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

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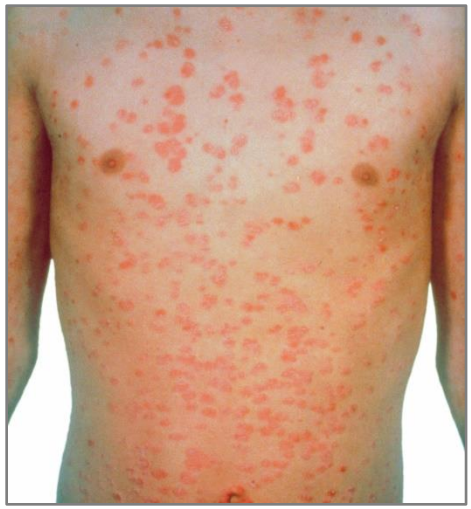
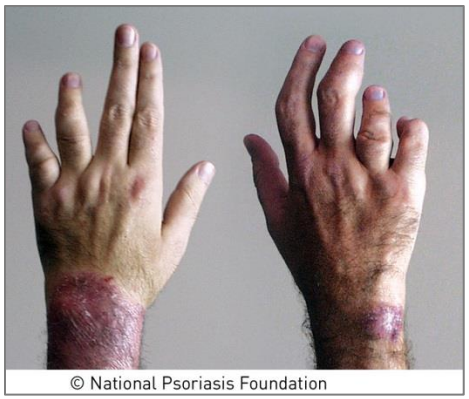
Challenges of Psoriatic Disease





© National Psoriasis Foundation

- **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

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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

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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?

Disease & Demographic / Age	Pre-adolescent (Parent)	Teen / College Student	Young Adult	Older American
Gender	Male Female + Pregnant/Trying	Male Female + Pregnant/Trying	Male Female + Pregnant/Trying	Male Female + Pregnant/Trying
Race/Ethnicity				
Skin Type	Normal Dry Oily Sensitive Combination	Normal Dry Oily Sensitive Combination	Normal Dry Oily Sensitive Combination	Normal Dry Oily Sensitive Combination
Severity	Mild Moderate Severe	Mild Moderate Severe	Mild Moderate Severe	Mild Moderate Severe
Years Since Diagnosis*	0-2 2-5 5-10 10+	0-2 2-5 5-10 10+	0-2 2-5 5-10 10+	0-2 2-5 5-10 10+
Geographic Distribution	Urban Suburban Rural	Urban Suburban Rural	Urban Suburban Rural	Urban Suburban Rural
Work Status	Working Limited work Unable to work/SSI	Working Limited work Unable to work/SSI	Working Limited work Unable to work/SSI	Working Limited work Unable to work/SSI
Socio-economic status^				
Health care provider	Rheumatologist Dermatologist Primary Care Provider Other None	Rheumatologist Dermatologist Primary Care Provider Other None	Rheumatologist Dermatologist Primary Care Provider Other None	Rheumatologist Dermatologist Primary Care Provider Other None
Treatment	Naïve/Not treating Topical Phototherapy Systemic Multiple	Naïve/Not treating Topical Phototherapy Systemic Multiple	Naïve/Not treating Topical Phototherapy Systemic Multiple	Naïve/Not treating Topical Phototherapy Systemic Multiple
Psoriasis +	Psoriasis only + Psoriatic Arthritis + Other chronic disease + Psoriatic Arthritis and other chronic disease	Psoriasis only + Psoriatic Arthritis + Other chronic disease + Psoriatic Arthritis and other chronic disease	Psoriasis only + Psoriatic Arthritis + Other chronic disease + Psoriatic Arthritis and other chronic disease	Psoriasis only + Psoriatic Arthritis + Other chronic disease + Psoriatic Arthritis and other chronic disease
Plaque Psoriasis (Scalp)				
Plaque Psoriasis (Face)				
Plaque Psoriasis (Other areas)				
Nail Psoriasis				
Guttate Psoriasis				
Inverse Psoriasis (Skin Folds)				
Inverse Psoriasis (Genitals)				
Pustular Psoriasis				
Erythrodermic Psoriasis				

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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.

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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.

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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

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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.

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"… 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?

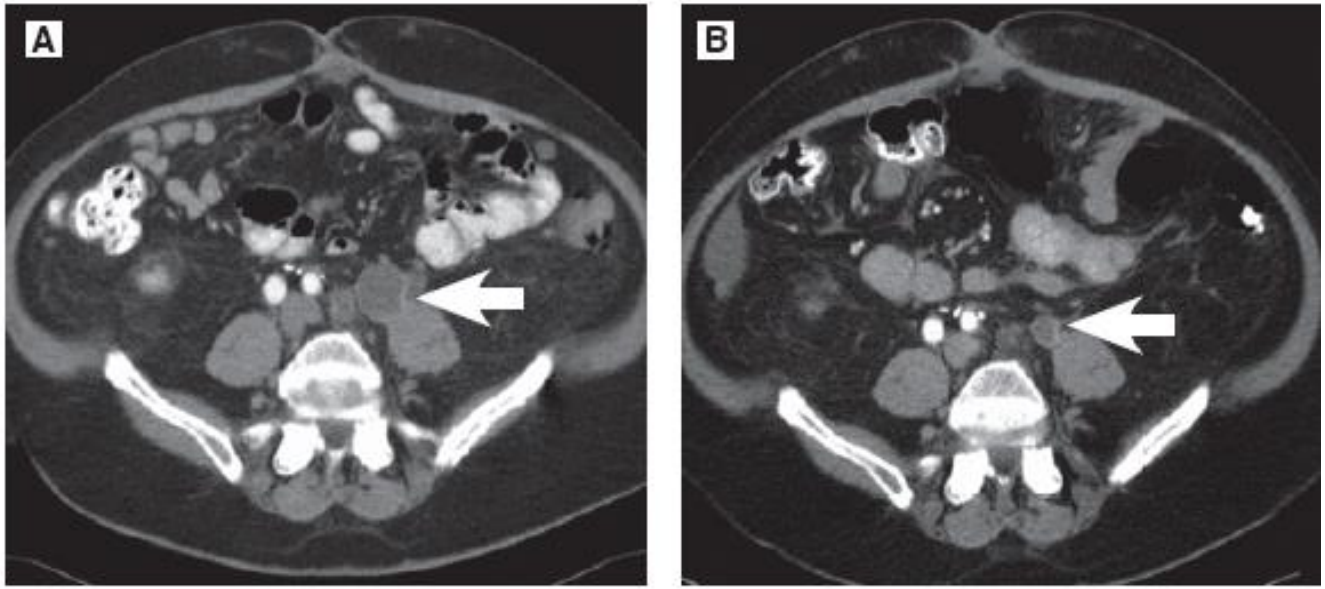


Figure 3: Response of Lymphadenopathy to Pazopanib – Computed tomography scan showing (white arrows) retroperitoneal lymphadenopathy **(A)** at baseline and **(B)** after nearly complete resolution with 4 months of pazopanib treatment. The patient had a confirmed partial response by Response Evaluation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

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

their symptom burden?

http://www.cancernetwork.com/testicular-cancer/response-antiangiogenesis-therapy-patient-advanced-adult-type-testicular-granulosa-cell-tumor

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 acneiform	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[a]	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)

Price T, et al. Eur J Cancer. 2016; 68:51-59.

Types of Clinical Outcome Assessments to Document Benefit:Risk

Concepts

Symptoms

Activities of daily living

Signs

Behaviors

Function
e.g., cognitive function, respiratory function

Measures

Patient

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.

Clinician

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.

Observer

A measurement reported by a parent, caregiver, or someone who observes the patient in daily life.

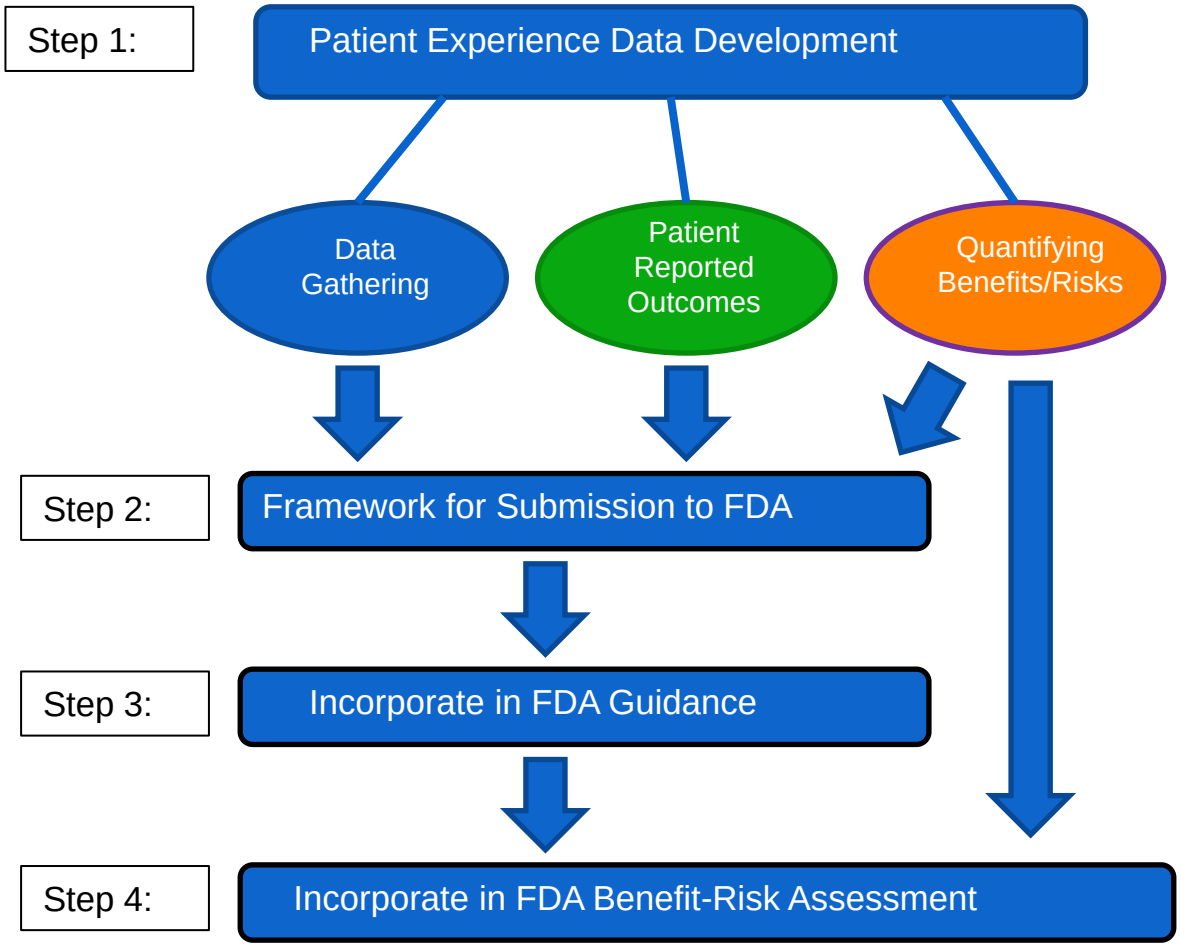
Test

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.

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

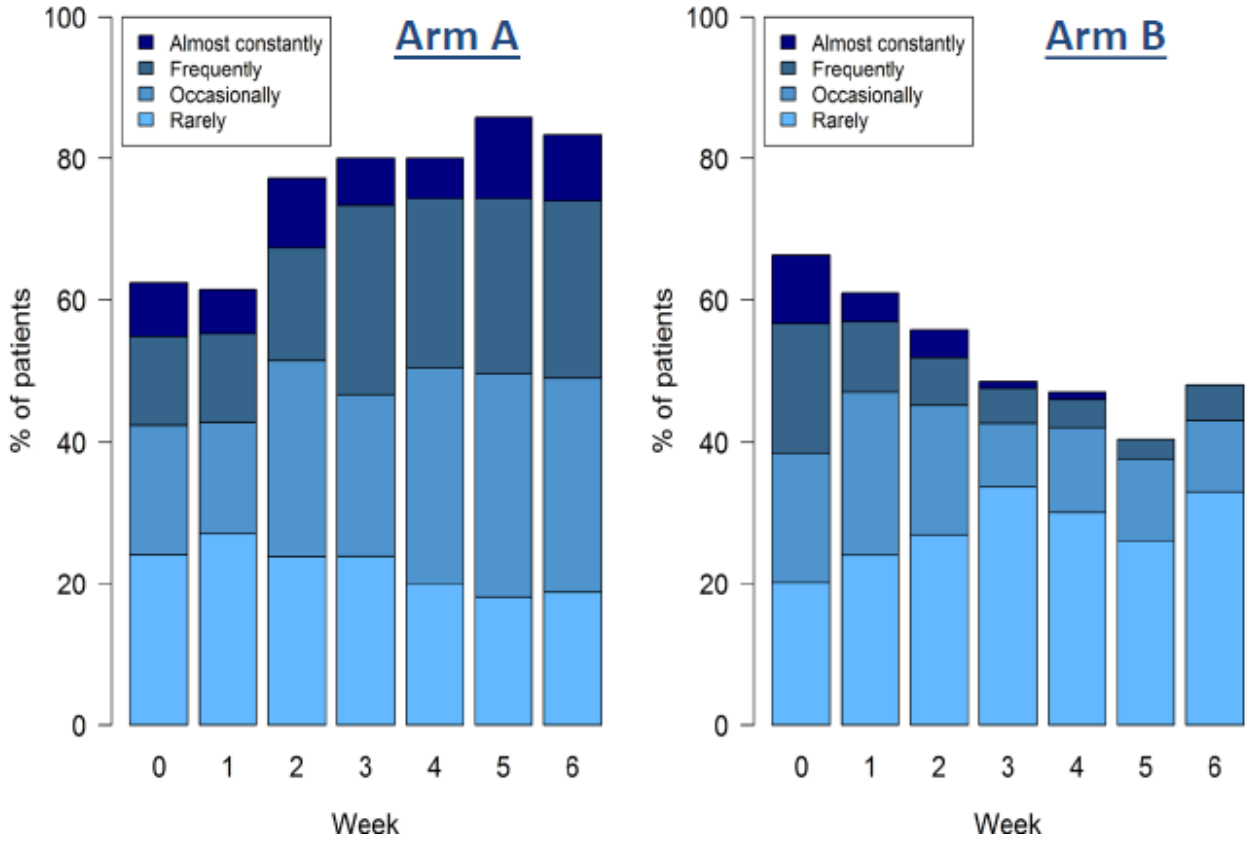


Is it Time for a Separate Patient Label ?

Patient Relevant Evidence Examples

PRO-CTCAE Distributions at Successive Time Points

Example: Diarrhea between Arms



Example: Patient Reported and Clinician Reported AE's

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

Table 5 Clinically graded and patient-reported adverse events for the 10 most common patient-reported adverse events

Symptomatic adverse event*	Any level (CTCAE grade or PRO-CTCAE score ≥1), n (%)			High level (CTCAE grade or PRO-CTCAE score† ≥3), n (%)		
	Supportive care (n=46)	Liquid honey (n=47)	Lozenge honey (n=47)	Supportive care (n=46)	Liquid honey (n=47)	Lozenge honey (n=47)
Anorexia						
CTCAE	11 (23.9%)	15 (31.9%)	5 (10.6%)	1 (2.2%)	-	1 (2.1%)
PRO-CTCAE						
Severity	35 (76.1%)	42 (89.4%)	42 (89.4%)	12 (26.1%)	11 (23.4%)	14 (29.8%)
Interference	25 (54.3%)	36 (76.6%)	34 (72.3%)	9 (19.6%)	12 (25.5%)	13 (27.7%)
Anxiety						
CTCAE	4 (8.7%)	4 (8.5%)	2 (4.3%)	-	-	-
PRO-CTCAE						
Frequency	34 (73.9%)	41 (87.2%)	44 (93.6%)	10 (21.7%)	12 (25.5%)	13 (27.7%)
Severity	33 (71.7%)	40 (85.1%)	44 (93.6%)	9 (19.6%)	10 (21.3%)	9 (19.1%)
Interference	23 (50%)	29 (61.7%)	26 (55.3%)	7 (15.2%)	8 (17%)	9 (19.1%)
Cough						
CTCAE	14 (30.4%)	21 (44.7%)	11 (23.4%)	-	1 (2.1%)	-
PRO-CTCAE						
Severity	43 (93.5%)	44 (93.6%)	44 (93.6%)	12 (26.1%)	12 (25.5%)	5 (10.6%)
Interference	28 (60.9%)	34 (72.3%)	33 (70.2%)	9 (19.6%)	11 (23.4%)	4 (8.5%)

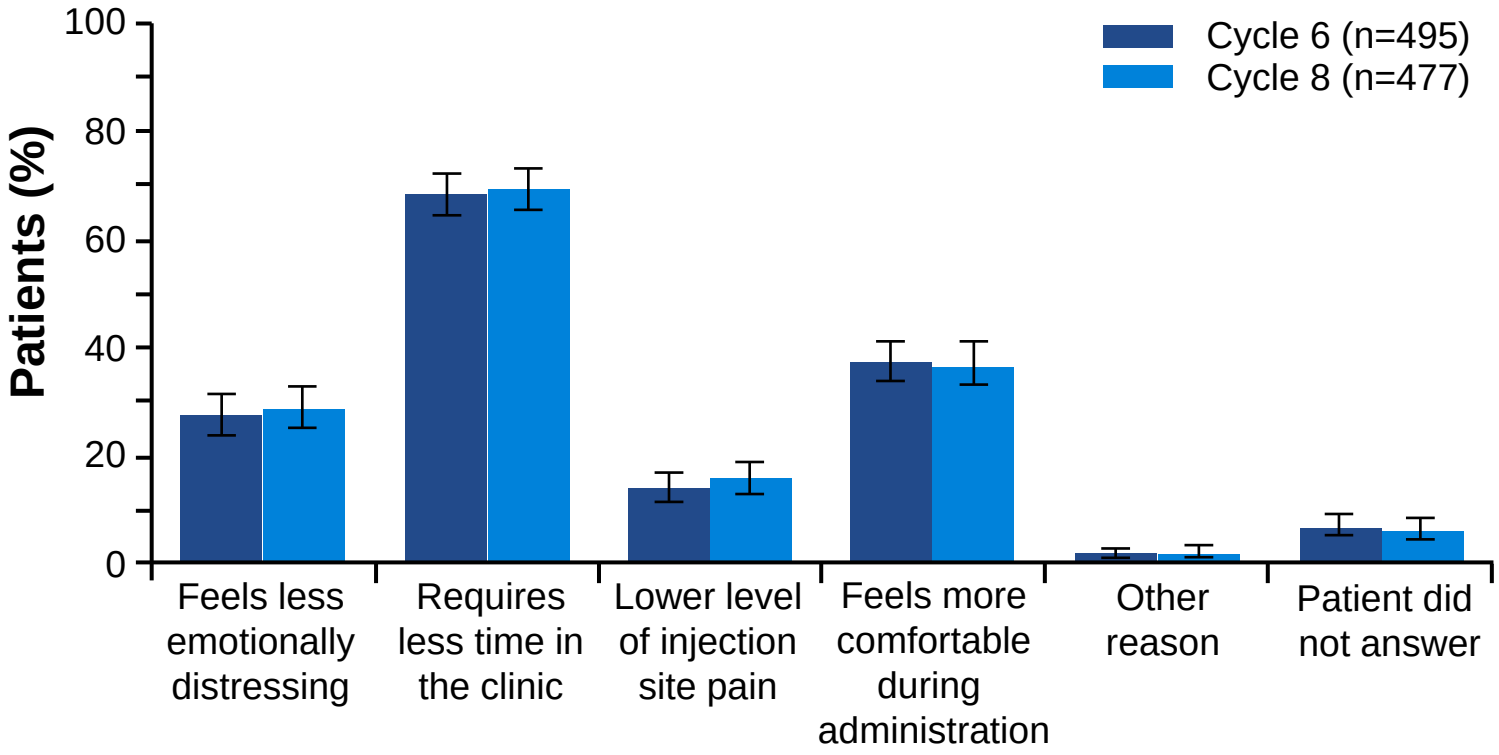
Abbreviations: CTCAE = Common Terminology Criteria for Adverse Events; PRO-CTCAE = Patient-Reported Outcome of the CTCAE.

* 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."

Fogh et al., Red Journal 2017

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“.

Rummel et al Annals of Oncology 28: 836–842, 2017 doi:10.1093/annonc/mdw685

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 with the upcoming PDUFA VI patient centricity guidances, as well as expanded use of patient preference methods will be key for success

U.S. FOOD & DRUG ADMINISTRATION

Session 2

Panel Discussion and Q&A

Pujita Vaidya
Facilitator

September 18, 2017

U.S. FOOD & DRUG ADMINISTRATION

BREAK

U.S. FOOD & DRUG ADMINISTRATION

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

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

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).[6-8] 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.[9] Differentiating between

Pennington, M., Gomes, M., & Donaldson, C. (2017). Handling protest responses in contingent valuation surveys. *Medical Decision Making*, 2017, *37*,623-634

Obscure Value-Laden Assumptions

Determinants of protest responses in environmental valuation: A meta-study

Jürgen Meyerhoff [a,*], Ulf Liebe [b,c]

Table 1
Predictors of protesting used in the analysis.

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

Meyerhoff, J., & Liebe, U. (2010). Determinants of protest responses in environmental valuation. *Ecological Economics, 70*, 366-374.

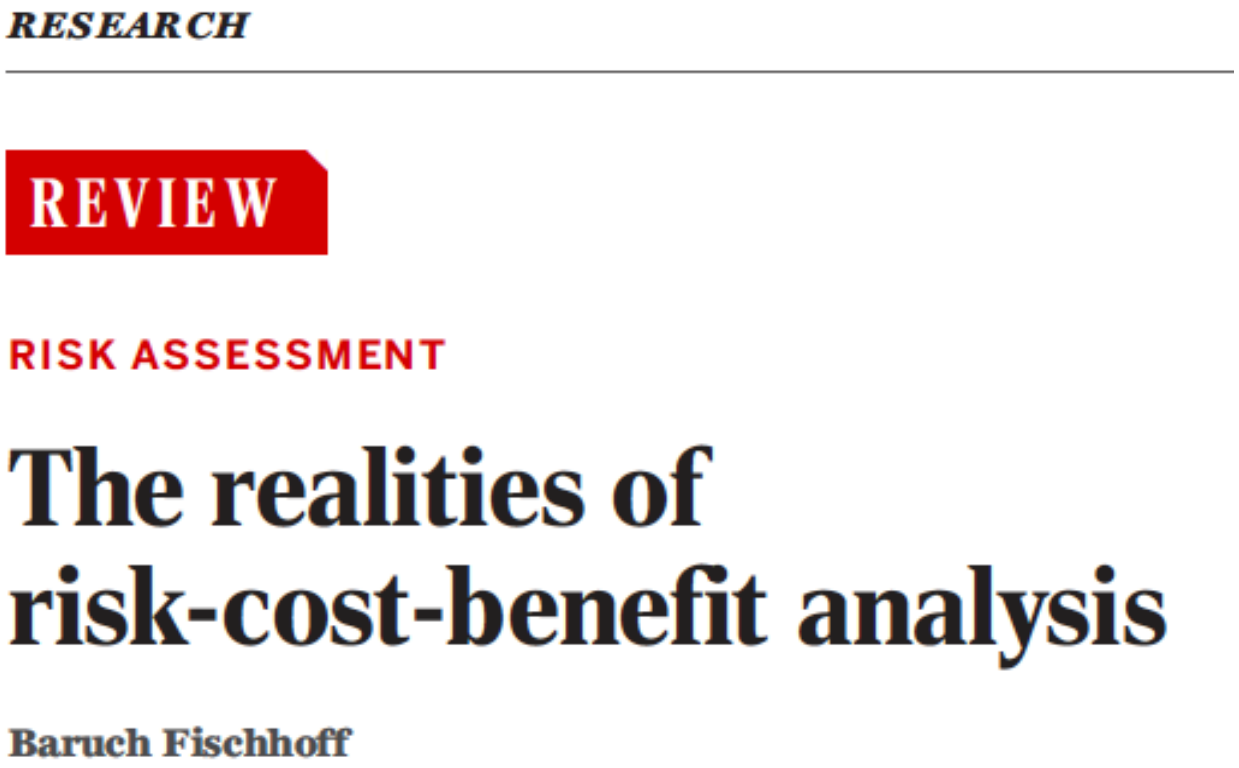
Obscure Value-Laden Assumptions

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


RESEARCH

REVIEW

RISK ASSESSMENT

The realities of risk-cost-benefit analysis

Baruch Fischhoff

http://dx.doi.org/10.1126/science.aaa6516

Frustrate Orderly Responses

REVIEW

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 valued fewer than 3 health states or 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[a]
All states valued the same
Fewer than *x* health states valued[b]
More than *x* logical inconsistencies[c]
Incomplete/missing data
Dead > all/several states
Dead ≥ 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)

Frustrate Orderly Responses

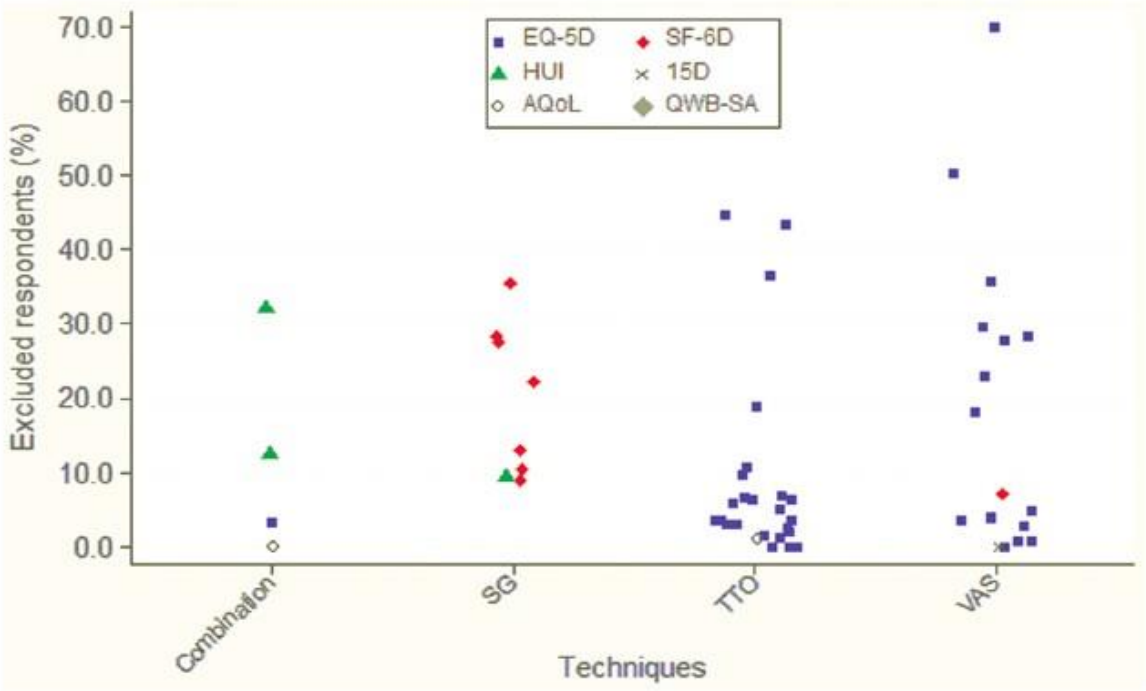
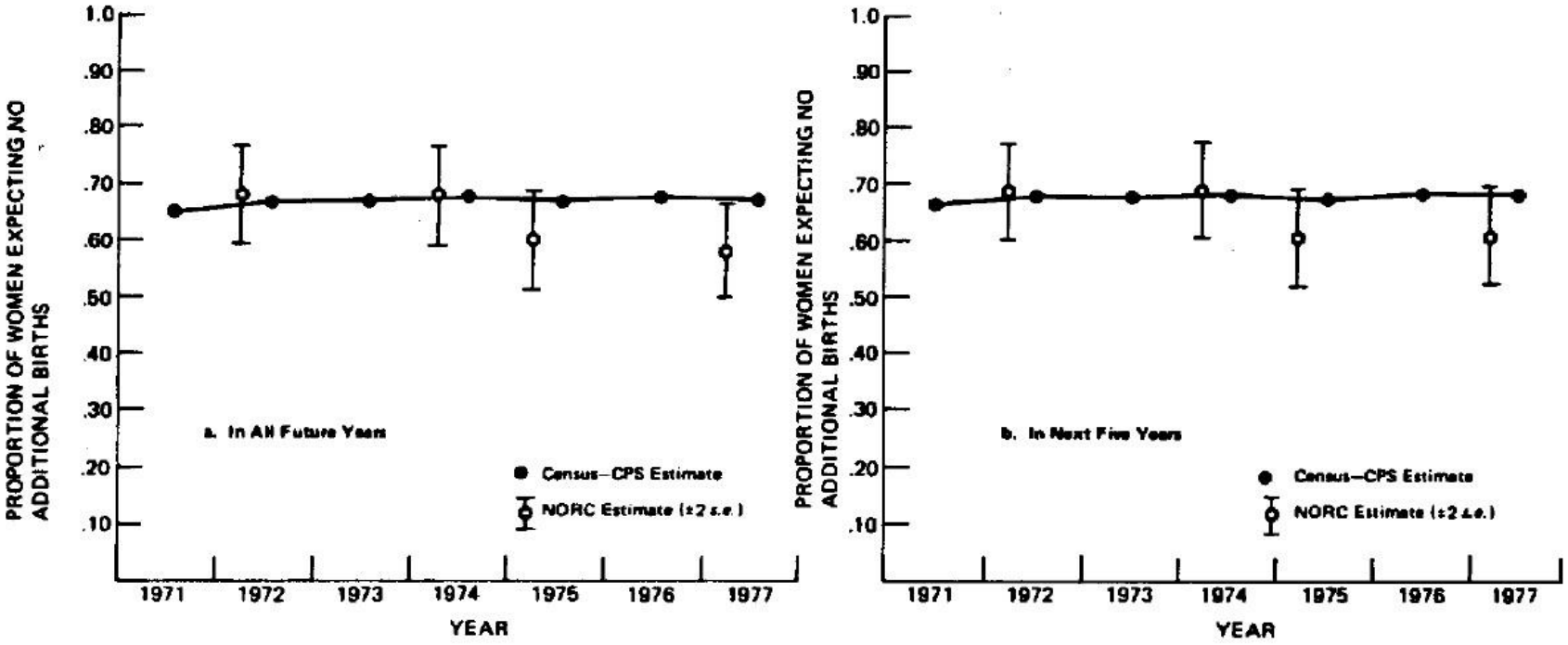


Figure 2 Proportion of excluded respondents, by valuation technique, with different markers used to indicate different preference-based health-related quality of life instruments (n = 55). The proportion of excluded respondents was reported in 55 (72%) studies, ranging from 0% to 65%. No exclusion rates 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.

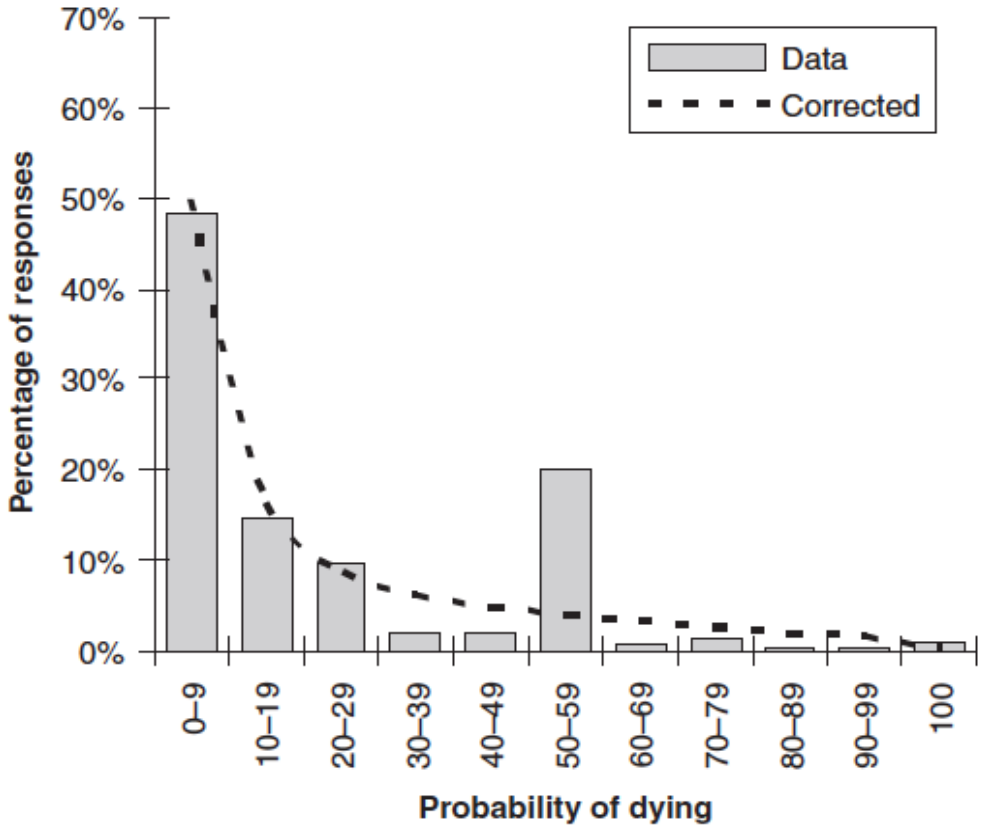
Misrepresent Respondents

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.



Note. Samples included only married women aged 18–39; sample sizes in each year were approximately 4,000 (Census-CPS) and 220 (NORC). CPS = Current Population Survey; NORC = National Opinion Research Center. From "Why Do Surveys Disagree? Some Preliminary Hypotheses and Some Disagreeable Examples" (p. 192) by C. F. Turner, 1984, in C. F. Turner and E. Martin, *Surveying Subjective Phenomena*, New York: Russell Sage Foundation. Copyright 1984 by the Russell Sage Foundation. Reprinted by permission.

Misrepresent Respondents



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

Fischhoff, B., & Kadvany, J. (2011). Risk: A very short introduction. Oxford: Oxford University Press

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[1]

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.

Morgan, M.G. (2014). Use (and abuse) of expert elicitation in support of policy making for public policy.
PNAS, 111, 7176-7186. http://www.pnas.org/content/111/20/7176

Consult Literature Broadly (Values)

Chapter 18

COGNITIVE PROCESSES IN STATED PREFERENCE METHODS

BARUCH FISCHHOFF

Department of Social and Decision Sciences, Department of Engineering and Public Policy, Carnegie Mellon University, Pittsburgh, PA 15213-3890, USA

Contents

Fischhoff, B. (2005). Cognitive processes in stated preference methods. In K.-G. Mäler & J. Vincent (eds.),
Handbook of Environmental Economics (pp. 937-968). Amsterdam: Elsevier

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

Figure 1: FDA Benefit-Risk Framework

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

FDA. (2013). *Structured approach to benefit-risk assessment for drug regulatory decision making*.
Draft PDUFA V implementation plan (2/13). FY2013-2017.

Decision Science Principles in FDA's Benefit-Risk Framework

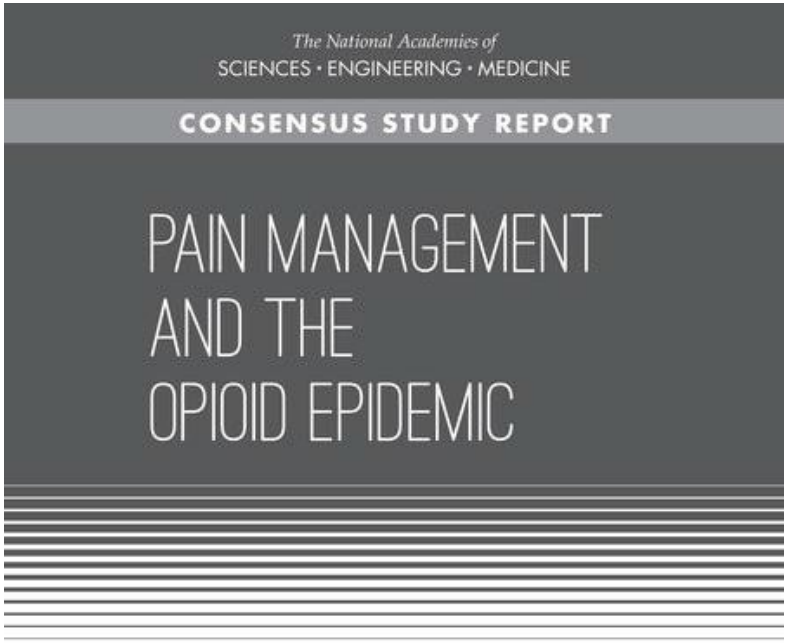
Recognizes scientific and policy judgment in all analyses

Quantifies the quantifiable, without ignoring other concerns

Highlights ethical and political tradeoffs, rather than burying them in a metric

Supports risk management

Fischhoff, B. (2017). Breaking ground for psychological science: The U.S. Food and Drug Administration. *American Psychologist, 72(2),* 118-125.



National Research Council. (2017). *Pain management and the opioid epidemic: Balancing societal and individual benefits of prescription opioid use*. Washington, DC: National Academy Press.

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

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Characteristics of Opioid		
How Opioid Fits among Currently Available Pain Treatment Options		
Benefits Observed in Clinical Trials, Overall • Benefits to patients • Public health benefits		
Risks Observed in Clinical Trials • Risks to patients • Public health risks		
Predicted Benefits/Risks to Families of Patients		
Predicted Benefits/Risks to Society, Overall • Special communities • Subpopulations		
Diversion Potential		
Predicted Effects on Use of Other Opioids or Illicit Drugs		
Risk Management, Overall • Potential for off-label use • Advertising/promotion		

National Research Council. (2017). *Pain management and the opioid epidemic: Balancing societal and individual benefits of prescription opioid use*. Washington, DC: National Academy Press.

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 Silver[2,4]

R_0: If someone gets Ebola in the US, how many people do you think will catch it from them directly?

Fischhoff, B., Wong-Parodi, G., Garfin, D., Silver, R., & Holman, E.A. (in press). Public understanding of Ebola risks: Mastering an unfamiliar threat. *Risk Analysis*. doi: 10.1111/risa.12794

Evaluate Critically; Report Candidly

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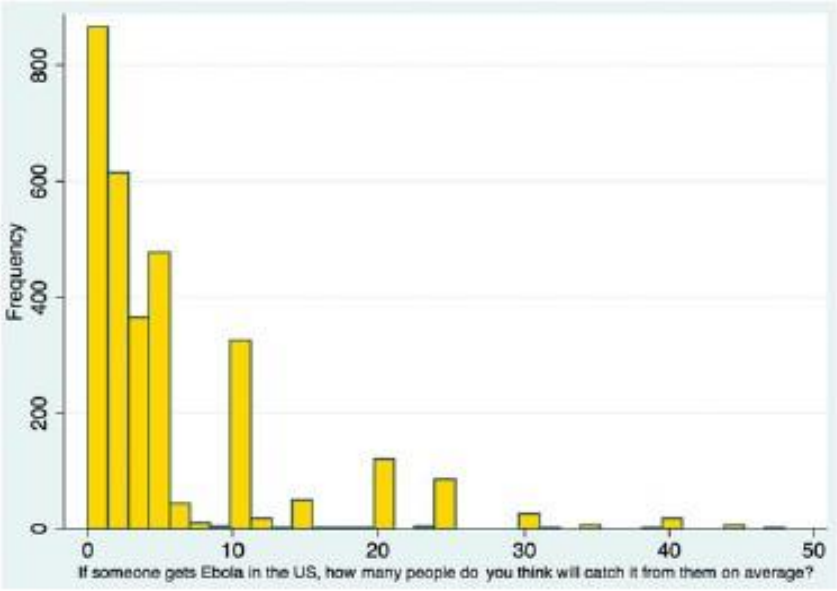
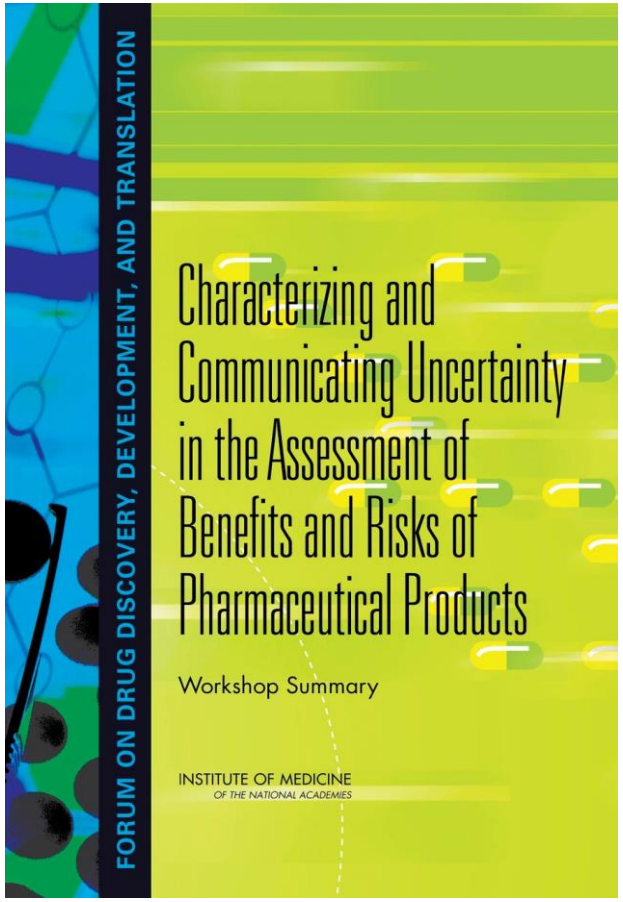


Fig. 1. Judgments of R_0 (pooling values used by <1% of respondents).

Fischhoff, B., Wong-Parodi, G., Garfin, D., Silver, R., & Holman, E.A. (in press). Public understanding of Ebola risks: Mastering an unfamiliar threat. *Risk Analysis*. doi: 10.1111/risa.12794

A Frontier: Uncertainty



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

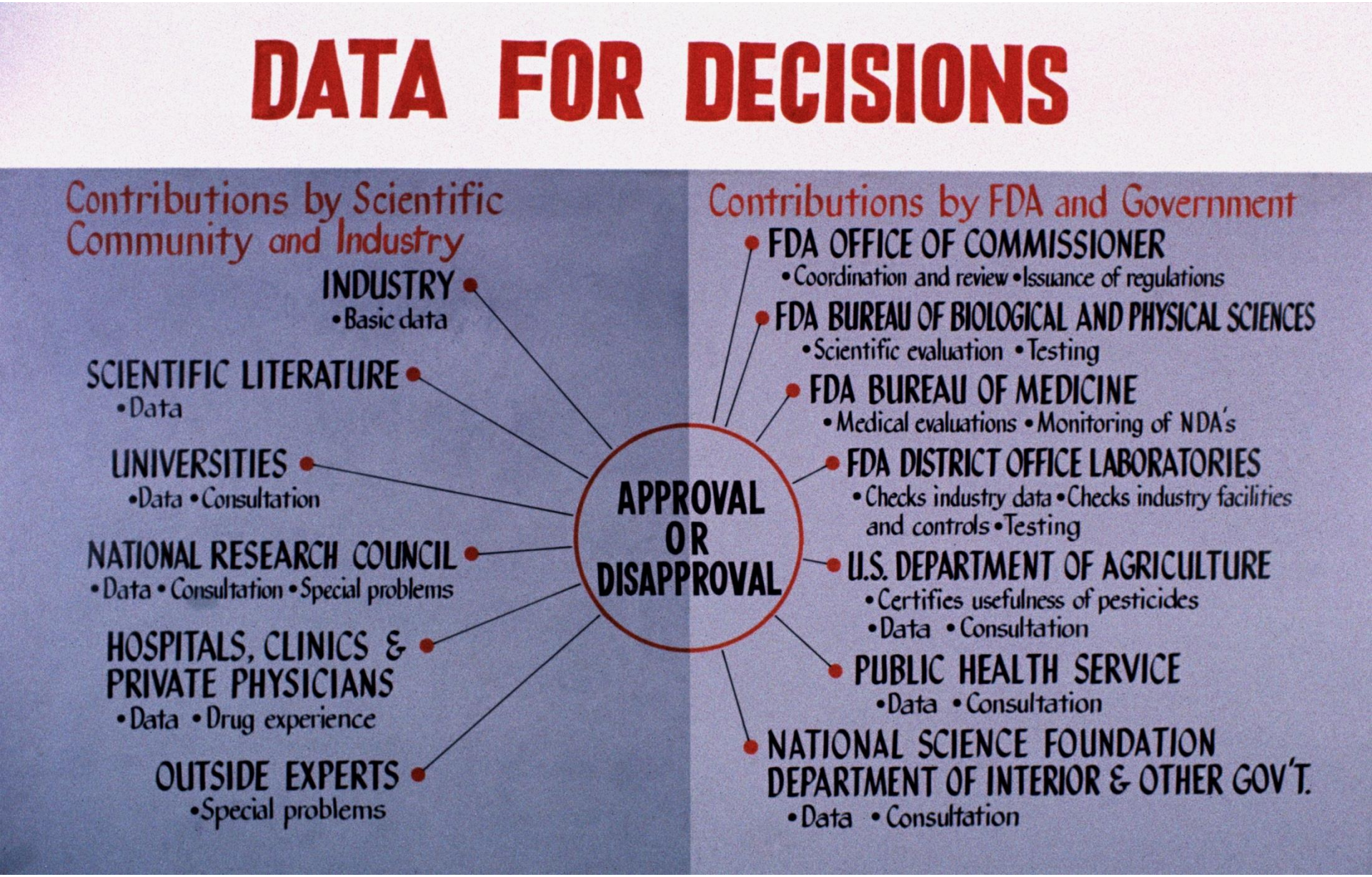
Fischhoff, B., & Davis, A.L. (2014). Communicating scientific uncertainty. *PNAS, 111*, 13664-13671. www.pnas.org/cgi/doi/10.1073/pnas.1317504111

Potential Areas for Quantitative Benefit-Risk Assessments

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

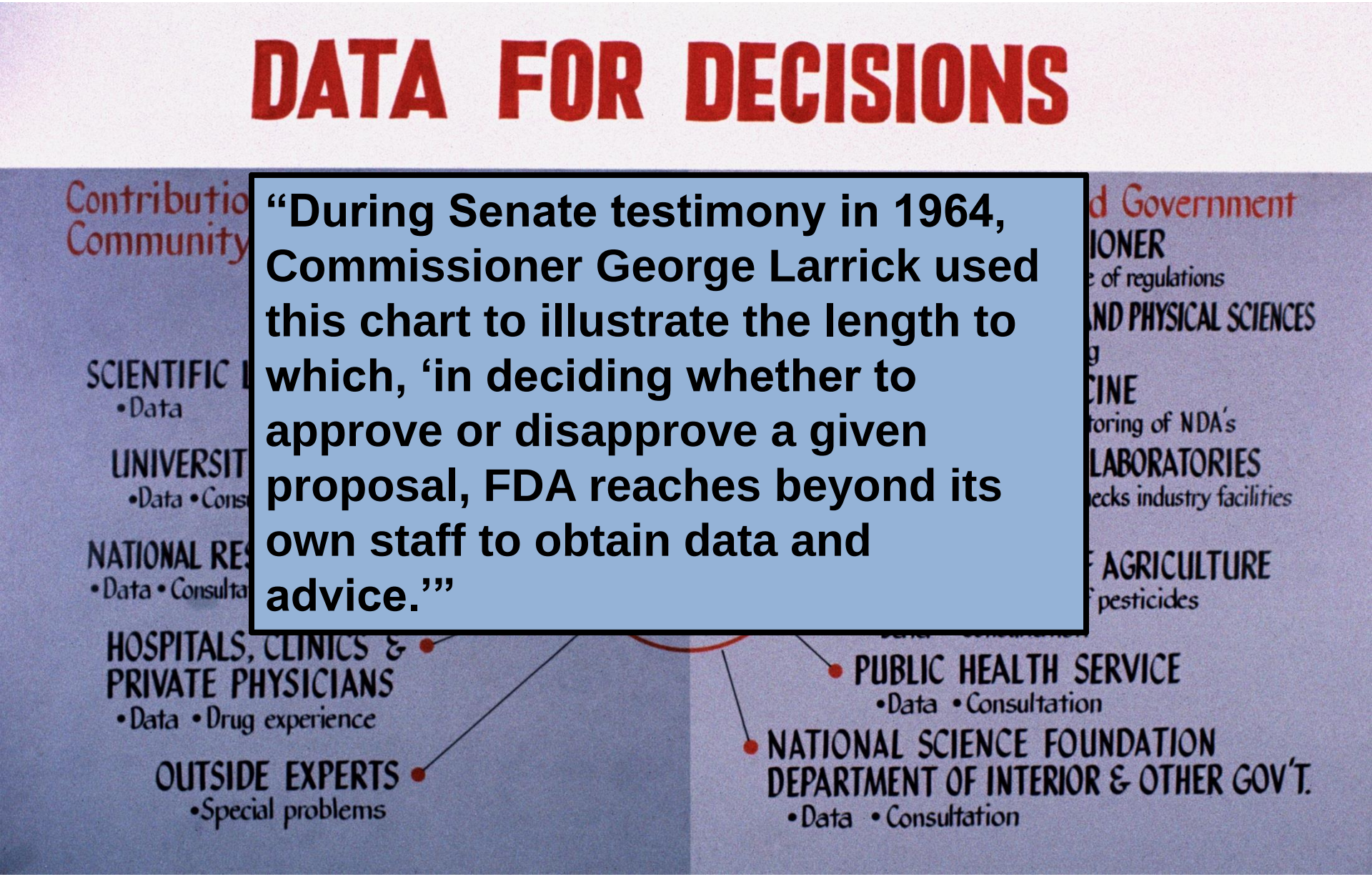
September 18, 2017

FDA Must Consider Many Types of Data From Many Sources



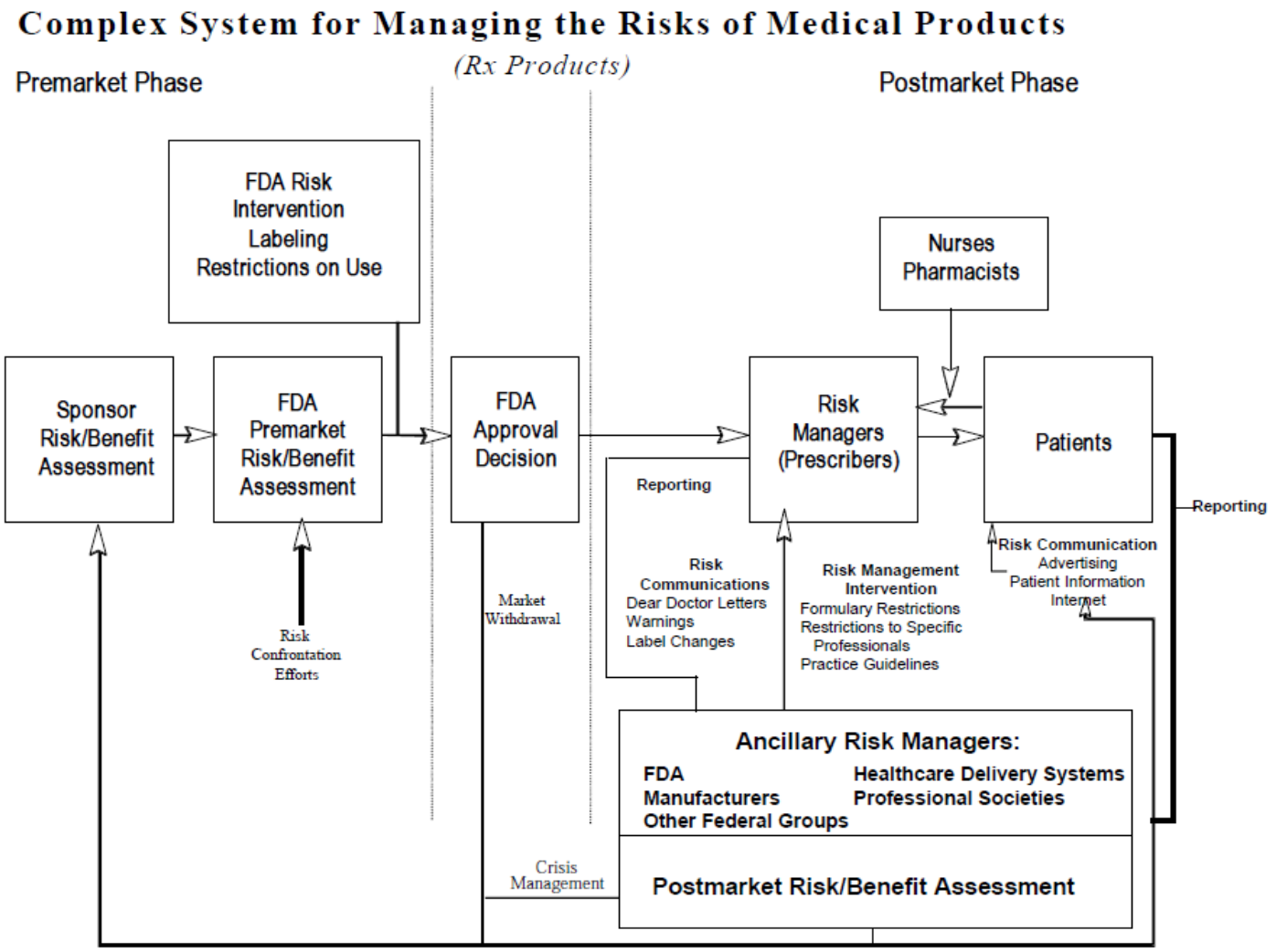
https://www.flickr.com/photos/fdaphotos/8205558579/in/album-72157624615595535/

FDA Must Consider Many Types of Data From Many Sources



"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.'"

https://www.flickr.com/photos/fdaphotos/8205558579/in/album-72157624615595535/



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

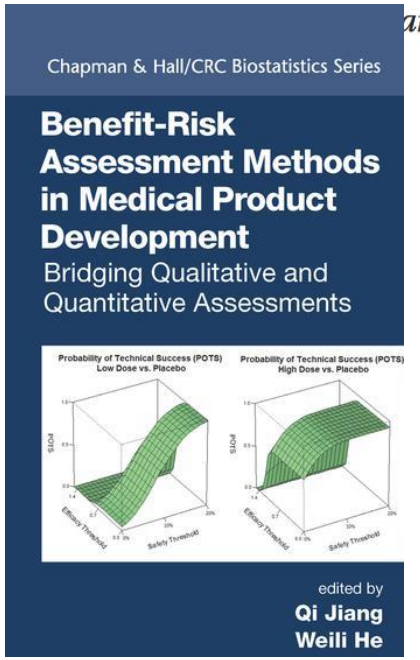
- Analytics and Benefit-Risk Assessment (ABRA) team in CBER/OBE
- Several quantitative benefit-risk assessments have been presented at Advisory Committees and published
- Engaged in internal and external training

TRANSFUSION

CONFERENCE REPORT

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, an E. Williams, Jay S. Epstein, and Steven A. Anderson



8

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

ICH BR Expert Working Group
Lisbon, Portugal 2016

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

ICH M4E(R2),

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

U.S. FOOD & DRUG ADMINISTRATION

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

Richard Forshee

Richard.Forshee@fda.hhs.gov

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

THE DARTMOUTH INSTITUTE
FOR HEALTH POLICY & CLINICAL PRACTICE
Where Knowledge Informs Change ™

GEISEL SCHOOL OF MEDICINE
AT DARTMOUTH

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

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.

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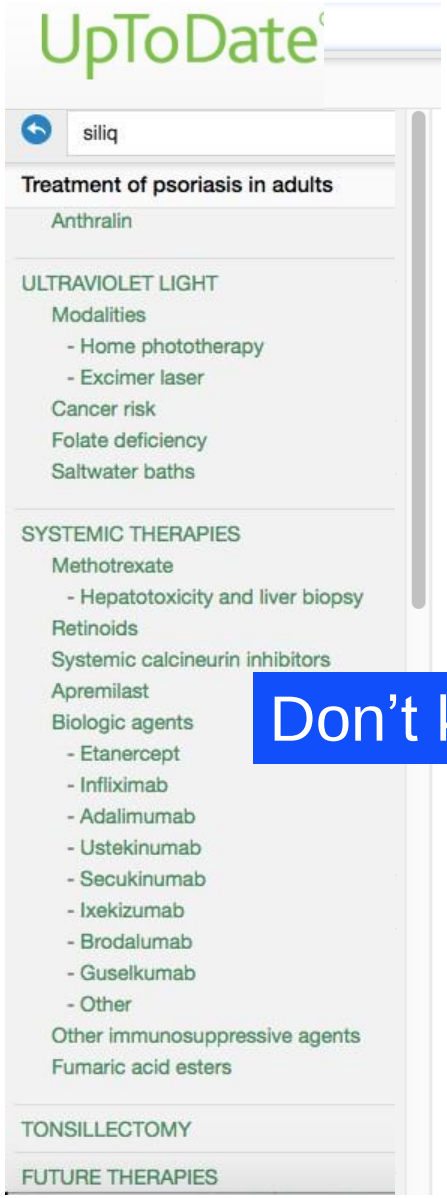

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Drug works well

Don’t know how worried to be about suicidality

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Phase 3 Studies Comparing Brodalumab with Ustekinumab in Psoriasis

CONCLUSION

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

Suicide not mentioned in abstract

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

Table 3. Maintenance of Clinical Response to Brodalumab at Week 52.*

Variable	AMAGINE-2				AMAGINE-3			
	140 mg every 8 wk (N=168)	140 mg every 4 wk (N=335)	140 mg every 2 wk (N=337)	210 mg every 2 wk (N=334)	140 mg every 8 wk (N=174)	140 mg every 4 wk (N=341)	140 mg every 2 wk (N=343)	210 mg every 2 wk (N=342)
sPGA score of 0 or 1 — no.	8	30	144	209	10	53	154	208
% (95% CI)	5 (2–9)	9 (6–13)	43 (37–48)	63 (57–68)	6 (3–10)	16 (12–20)	45 (40–50)	61 (55–66)
Adjusted P value†								
vs. 140 mg every 8 wk	—	—	<0.001	<0.001	—	—	<0.001	<0.001
vs. 140 mg every 4 wk	—	—	<0.001	<0.001	—	—	<0.001	<0.001
vs. 140 mg every 2 wk	—	—	—	<0.001	—	—	—	<0.001

* In the statistical analysis, missing data and data from patients who did not have an adequate response (i.e., who had an sPGA score ≥3 or persistent sPGA scores of 2 over at least a 4-week period) through week 52 were imputed as nonresponses at the time at which the judgment regarding an inadequate response was made. N values are the numbers of patients who underwent rerandomization and had a valid measurement value at week 52, after imputation.
†We calculated the adjusted P value by applying the sequential testing procedure for multiplicity adjustment at a significance level of 0.05.

1.5 in the AMAGINE-3 study; the corresponding rates with ustekinumab were 0.8 and 0.8 (Tables S11 and S12 in the Supplementary Appendix). Candida infections occurred more frequently with brodalumab than with ustekinumab or placebo during the induction phase (Table S10 in the Supplementary Appendix); all the infections were graded as mild or moderate, and none were systemic. This trend continued through week 52 (Tables S11 and S12 in the Supplementary Appendix). One case of Crohn's disease occurred during the maintenance phase (Tables S11 and S12 in the Supplementary Appendix). The rates of serious infectious episodes per 100 patient-years of exposure to brodalumab through week 52 were 1.0 in the AMAGINE-2 study and 1.3 in the AMAGINE-3 study; the corresponding rates with ustekinumab were 0.8 and 1.2 (Tables S11 and S12 in the Supplementary Appendix).

One death (from stroke) occurred during the induction phase (in the AMAGINE-2 study, in a patient in the 210-mg brodalumab group, 20 days after the last dose), and five deaths occurred through week 52: in the AMAGINE-2 study, one from cardiac arrest (in a patient who received 210 mg of brodalumab continuously throughout the study) and one each from cardiac arrest and pancreatic carcinoma (in patients in the ustekinumab group), and in the AMAGINE-3 study, one from cardiac arrest (in a patient who had received 140 mg of brodalumab every 2 weeks followed by 210 mg) and one from accidental death in a motor vehicle accident (in a patient who had received 210 mg of brodalumab followed by 140 mg every 2 weeks). Three deaths occurred after exposure: in the AMAGINE-2 study, one from completed suicide (in a patient who had received placebo followed by 210 mg of brodalumab, 27 days after the last dose), and in the AMAGINE-3 study, one from the hematophagic histiocytosis syndrome (in a patient who had received 140 mg of brodalumab every 2 weeks followed by 140 mg every 4 weeks and rescue therapy, 41 days after the last dose) and one from cardiomyopathy (in a patient who had received 210 mg of brodalumab followed by 140 mg every 4 weeks and rescue therapy, 87 days after the last dose). There was one additional suicide after week 52 during the open-label extension (in the AMAGINE-2 study, in a patient who had received 210 mg of brodalumab every 2 weeks, 19 days after the last dose).

Immunogenicity

Anti-brodalumab antibodies (nonneutralizing) were detected during the period from baseline through week 52 in 28 brodalumab-treated patients (1.8%) in the AMAGINE-2 study and in 37 brodalumab-treated patients (2.3%) in the AMAGINE-3 study. None were associated with a loss of efficacy or adverse events. No patient had neutralizing antibodies. Nonneutralizing anti-brodalumab antibodies were detected in 4 patients at baseline. Among the patients who were randomly assigned to ustekinumab, samples from 6 patients after the initiation of ustekinumab

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

FDA Office Director Benefit-Risk Summary

"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**

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.

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

Benefit-Risk Summary and Assessment

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

Indication This m 1032 for Siliq (brodalumab) injec nts who are candidates for syst onse to other systemic therapies

Benefit The effica bo, Siliq 210 mg every 2 weeks de s with sPGA of 0 or 1 at Week 12 a ndary endpoints of PASI 100, and sP anged from 83% to 86% in r sPGA of 0 or 1 ranged from 76% t patients . The maximal effect of Siliq on s treatment from week 12 to week 1 ficacy of Siliq (brodalumab) is no o have failed prior biologic therapies, ous biologic psoriasis therapies trials, and PASI-90 and PASI-100 r limited treatment options, may be wi

Comparative effi of already approved psoriasis therapies, the additional benefits appear minimal. 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 mono

Information displayed inefficiently

- 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 p m, compared with none in placebo subjects;„across all clinical development p ms 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

	Trial 3			Trial 4		
Design	Double-blind, superiority			Double-blind, superiority		
Duration	12 weeks			12 weeks		
	Siliq n=612	**Stelara** n=300	**Placebo** n=309	**Siliq** n=624	**Stelara** n=313	**Placebo** n=311
Psoriasis better?	210mg SQ every 2 weeks	45mg SQ week 0 and 4	No drug SQ every 2 weeks	210mg SQ every 2 weeks	45mg SQ week 0 and 4	No drug SQ every 2 weeks
Primary outcomes						
Major improvement ≥ 75% improved psoriasis score - PASI 75	83%	70%	8%	85%	69%	6%
Minimal or no psoriasis Physician rated skin clear or almost clear - sPGA= 0/1	79%	61%	4%	80%	57%	4%
Secondary outcomes						
No psoriasis Physician rated skin clear - sPGA= 0	45%	21%	1%	37%	19%	<1%

Benefit

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

	Trial 3		
Design	Double-blind, superiority		
Duration	12 weeks		
Psoriasis better?	**Siliq** n=612 210mg SQ every 2 weeks	**Stelara** n=300 45mg SQ week 0 and 4	**Placebo** n=309 No drug SQ every 2 weeks
Primary outcomes **Major improvement** ≥ 75% improved psoriasis score - PASI 75	Pooled results		
Minimal or no psoriasis Physician rated skin clear or almost clear - sPGA= 0/1			
Secondary outcomes **No psoriasis** Physician rated skin clear - sPGA= 0			

Side effects

		All psoriasis trials combined		
		Siliq n=1,496	**Stelara** n=613	**Placebo** n=879
		210mg SQ every 2 weeks	45mg SQ week 0 and 4	
Black Box Warning	**Suicidal thoughts and behaviors including completed suicides**	4 suicides	0 suicides	0 suicides
Serious side effects	**Serious infection**	0.5%	0.3%	0.2%
	Over 12 weeks	1.3%	1.0%	
	Over 52 weeks	Seen in other trials		
	New Crohn's Disease Diagnosis **Tuberculosis reactivation**	1 person	0 people	0 le peop
Most common symptom side effects	**Arthralgia**	5%	2%	3 %
	Headache	4%	4%	4 %
	Fatigue	3%	3%	1 %
	Diarrhea	2%	1%	1 %
	Mouth or throat pain	2%	1%	1 %
	Myalgia	2%	1%	0.3 %
	Injection site reactions	2%	2%	1 %

The Drug Facts Box: Improving the communication of prescription drug information

Lisa M. Schwartz[1] and Steven Woloshin[1]

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 favor able trials, favorable outcomes within trials, and "spinning" unfa vorable 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. How ever, 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 un derstand the Drug Facts Box and that it improves decision-making. Despite calls from their own Risk Communication Advisory Commit tee and Congress (in the Affordable Care Act) to consider implement ing boxes, the FDA announced it needs at least 3-5 y more 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 in crease inappropriate demand for marginally effective drugs.

Current investment in DTC advertising is substantial. Pharma ceutical 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 adver tisements 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 market ing 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 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 illus trate 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 dis orders). 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

	Etanercept (Enbrel®)	Infliximab (Remicade®)	Adalimumab (Humira®)	Ustekinumab (Stelara®)	Ixekizumab (Taltz®)	Secukinumab (Cosentyx®)[b]	Brodalumab (Siliq®)
PASI 75	47%	79%	72%	72%	89%	78%	85%
PASI 100	NA	NA	NA	NA	37%	NA	41%
sPGA 0/1	51%[a]	85%[a]	63%[a]	68%[a]	82%	63%[a]	79%

Source: Clinical Review of Data from PI.

[a] sPGA clear (0) or minimal (1)

[b] Secukinumab only included PASI 90 (56%)

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   - Current treatment options

3. Summarize FDA review team approval votes and rationale

Should FDA approve [Siliq] for moderate-to-severe plaque psoriasis?

Primary FDA review: Division of Dermatology and Dental Products

Division Director	Yes	Reason Summary Review (PDF)
Team Leader	Yes	Reason Cross Discipline Team Leader Review (PDF)
Reviewer	No	Reason Medical Review (PDF)

Division of Psychiatry Products	No	Reason Review (PDF)
Division of Cardiac and Renal Products	Yes	Reason Review (PDF)
Division of Epidemiology	No	Reason Review (PDF)
Division of Pharmacovigilance	Yes	Reason Review (PDF)

Should FDA approve [Siliq] for moderate-to-severe plaque psoriasis?

Primary FDA review: Division of Dermatology and Dental Products

Division Director	Yes	Reason Summary Review (PDF)
Team Leader	Yes	Reason Cross Discipline Team Leader Review (PDF)
Reviewer	No	Reason

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

Division of Psychiatry P		Review (PDF)
Division of Cardiac and Renal Products	Yes	Reason Review (PDF)
Division of Epidemiology	No	Reason Review (PDF)
Division of Pharmacovigilance	Yes	Reason Review (PDF)

Routinely present agreement or disagreement to highlight whether important uncertainties exist

Division Director	Yes	Reason Summary Review (PDF)
Team Leader	Yes	Reason
Reviewer	No	

"…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

FDA consult reviews

Division of Psychiatry Pr		
Division of Cardiac and Renal Products	Yes	Reason Review (PDF)
Division of Epidemiology	No	Reason Review (PDF)
Division of Pharmacovigilance	Yes	Reason Review (PDF)

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
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   - 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.

Consumer

Prescribers

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.

MORE INFO

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DRUG TRIA

What is the dr

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What are the benefits of this drug (results of trials used to assess efficacy)?

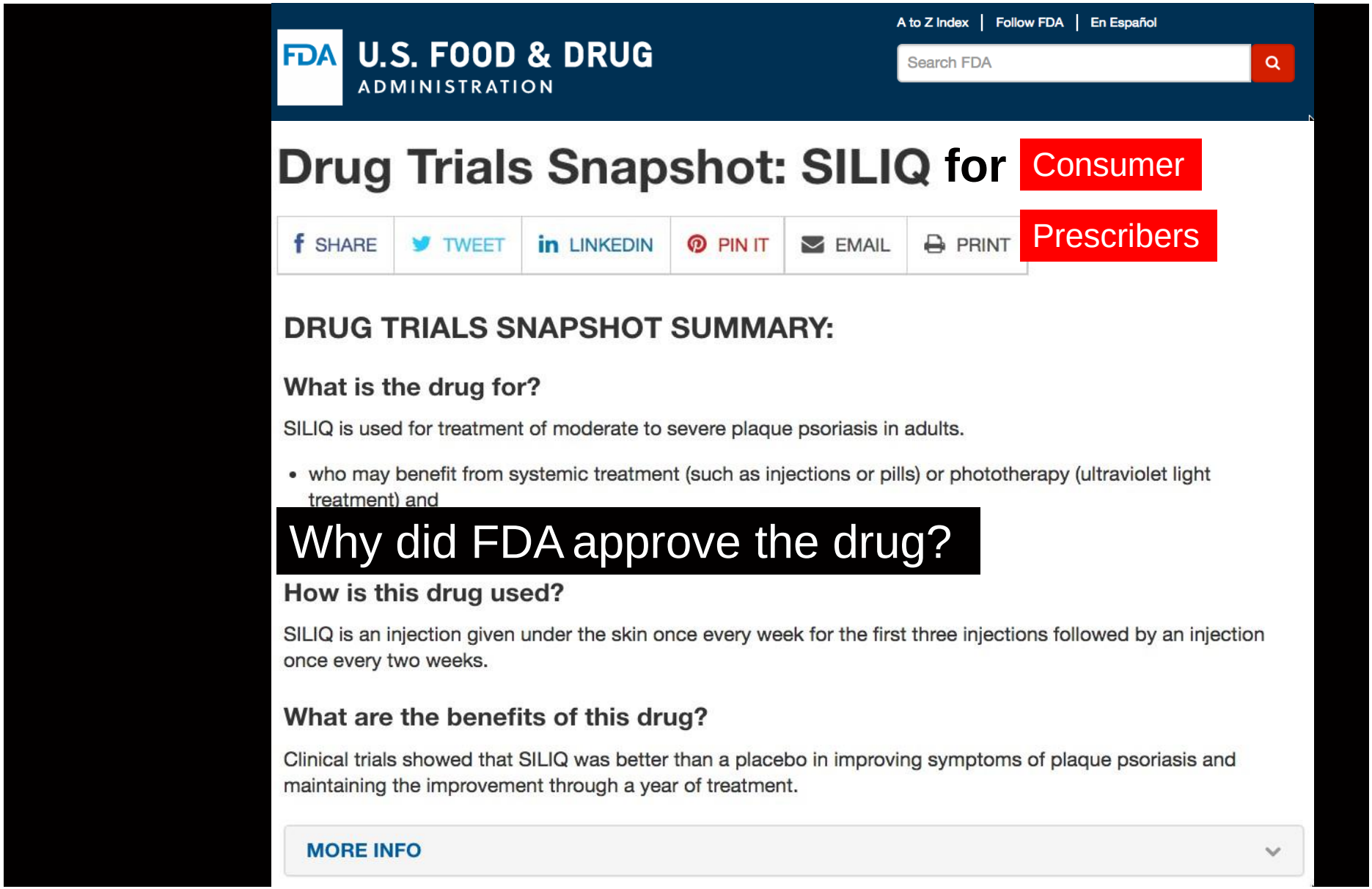
The table below summarizes efficacy results for the clinical trials based on the two co-primary endpoints: 1) PASI 75, the proportion of subjects who achieved at least a 75% reduction in the Psoriasis Area and Severity Index (PASI) composite score that takes into consideration both the percentage of 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[a]

Endpoint	Trial 1		Trial 2			Trial 3		
	SILIQ (N=222) n (%)	Placebo (N=220) n (%)	SILIQ (N=612) n (%)	Ustekinumab (N=300) n (%)	Placebo (N=309) n (%)	SILIQ (N=624) n (%)	Ustekinumab (N=313) n (%)	Placet (N=31 n (%)
PASI 75[b] response	185 (83)	6 (3)	528 (86)	210 (70)	25 (8)	531 (85)	217 (69)	19 (6)
PASI 100 response	93 (42)	1 (<1)	272 (44) [a]	65 (22)	2 (1)	229 (37)[a]	58 (19)	1 (<1)
sPGA success clear (0) or almost clear (1)[b]	168 (76)	3 (1)	481 (79)	183 (61)	12 (4)	497 (80)	179 (57)	13 (4)
sPGA of clear (0)	93 (42)	1 (<1)	274 (45)	65 (21)	2 (1)	229 (37)	58 (19)	1 (<1)

[a] NRI=non-responder imputation
[b] Co-primary endpoints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Drug Trials Snapshot: SILIQ for
Consumer
Prescribers
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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?
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.
MORE INFO

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.

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Session 3

Panel Discussion and Q&A

Sara Eggers
Facilitator

September 18, 2017

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Open Public Comment

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

September 18, 2017

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Closing Remarks

Theresa Mullin, Ph.D.
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U.S. Food and Drug Administration

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