

Characterizing FDA's Approach to Benefit-Risk Assessment throughout the Medical Product Life Cycle

Tommy Douglas Conference Center • Silver Spring, MD

May 16th, 2019

9:00 am – 4:55 pm

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ICA U.S. FOOD & DRUG



Benefit-Risk Assessment at CBER

Bichard Forshee, PhD

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Duke-Margolic Center for Health Policy May 16, 2010





Benefit Risk Assessment: Incorporating the Patient Perspective

Theresa V. Strong, PhD Director of Research Programs Foundation for Proder Willi Research





Office of Pharmocovigilance and Epidemiology Office of Surveillance and Epidemiology Center of Drug Evaluation and Research.

USING BENEFIT-RISK to

INFORM FDA and SPONSOR

DECISION- MAKING in the

POST- MARKETING SETTING

Characterizing FDA's Approach to Benefit-Risk Assessment throughout the Medical Product Life Cycle

Using Genefit-Risk Assessment to leform FGA and Sponsor Decision-Making in the Post-Marketing Setting

Juhaeri Juhaeri Head, Epidemiology and Benefit - Risk



Duke-FDA Benefit-Risk Assessment Silver Spring, MD May 16, 2019



Johnson-Achnson

Public Meeting: Characterizing FDA's Approach to Benefit-Risk Assessment throughout the Medical Product Life Cycle

Challenges to Advancing Structured Benefit-risk Assessment and Potential Next Steps

Bennett Levitan, MD-PhD Benefit-Risk Team Lead Department of Epidemiology Janssen Research & Development, LLC

OFFICE OF THE CHIEF MEDICAL OFFICER

May 16, 2019







Welcome & Overview

Dr. Mark McClellan, MD, PhD, Director, Duke-Margolis Center for Health Policy 9:00 am – 9:05 am



Electronic Comments

Federal eRulemaking Portal

Docket ID: FDA-2019-N-1468

Due June 17, 2019 11:59 PM ET

www.regulations.gov/docket?D=FDA-2019-N-1468



Opening Remarks

Theresa Mullin, PhD, Associate Director for Strategic Initiatives

Center for Drug Evaluation and Research (CDER)

9:05 am - 9:15 am





Applying Framework for Benefit-Risk Assessment Throughout the Human Drug Life Cycle

Opening Remarks

Theresa Mullin, PhD
Associate Director Strategic Initiatives
FDA Center for Drug Evaluation and Research

Context



- FDA qualitative structured B-R framework primarily discussed in context of premarket assessment
- PDUFA VI (FDARA 2017) enhancing benefit-risk assessment in regulatory decision-making
 - FDA will further the agency's implementation of structured benefit-risk assessment, including the incorporation of the patient's voice in drug development and decision-making, in the human drug review program
 - FY 2019 -- FDA will convene a meeting, conducted through a qualified third party, to gather industry, patient, researcher, and other stakeholder input on key topics.
 - Including applying the benefit-risk framework throughout the human drug lifecycle, including best approaches to communicating FDA's benefit-risk assessment
 - FY 2020, FDA will publish a draft guidance on benefit-risk assessments for new drugs and biologics



Benefit-risk guidance topics

From PDUFA VI:

- Articulate FDA's decision-making context and framework for benefit-risk assessment throughout the human drug lifecycle
- Discuss appropriate interactions between sponsors and FDA during drug development to understand the therapeutic context for regulatory decisions
- Discuss appropriate approaches to communicate to the public FDA's thinking on a product's benefit-risk assessment, such as through using the B-R framework at AC meetings
- From 21 CC: discuss how patient experience data can be used to inform benefit-risk assessment



21st Century Cures Act

- 21st Century Cures Act (2016) Title III Section 3002 requires FDA to issue new guidance regarding methods and approaches to be used in capturing and measuring patients' experiences and perspectives including guidance on:
 - "how the Secretary, if appropriate, anticipates using relevant patient experience data and related information, including with respect to the structured risk-benefit assessment framework described in section 505(d) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(d)), to inform regulatory decision making" Section 3002 (c)(8)





FDA's Patient-Focused Drug Development

https://www.fda.gov/Drugs/DevelopmentApprovalProcess/ucm579400.htm



- Patients are experts on living with their disease
- Their input can inform throughout lifecycle,
 e.g.,:
 - The therapeutic context
 - The potential benefits that are most meaningful
 - The acceptability of risk and uncertainty
 - The value and burden of risk minimization efforts
 - How a product's B-R profile changes in light of new information about benefits or risks
- FDA and others are advancing systematic approaches to capture and incorporate patient experience and perspectives

FDA Discussion Document Outlined Planned Approach to this Guidance



- Decisions and activities undertaken by Sponsors in development of their products— and evidence generated to support their marketing application—can have a significant impact on the ultimate benefit-risk assessment that support drug regulatory decision-making.
- Intent of planned benefit-risk guidance is to provide sponsors and other stakeholders with a clearer understanding of how considerations on a drug's benefits, risks, and uncertainties factor into FDA's regulatory decisions about the marketing authorization of a drug
- This understanding can help inform sponsors' decisions about their drug development programs and the evidence they generate in support of their new drug applications or biologics licensing applications.

Today's Meeting



- Three sessions featuring FDA considerations and panel discussions on:
 - 1. How evidence generated by Sponsor in their drug development programs can best inform the benefit-risk assessment of a marketing application
 - Considering stages and milestones in "life cycle" and how drug development activities can inform benefit-risk assessments.
 - 2. How benefit and risk information can be effectively communicated to support benefit-risk assessments; and
 - 3. How benefit-risk assessment inform FDA and sponsor decision-making in the post-market setting.
- Session panels and public comments will provide valuable input to FDA in development of this guidance



We look forward to today's discussion!

Introduction: FDA's approach to Benefit-Risk Assessment

Sara Eggers, PhD & Kerry Jo Lee, MD, U.S. Food & Drug Administration 9:15 am – 10:00 am





Introduction FDA's Approach to Benefit-Risk Assessment in Human Drug Review

Sara Eggers, PhD

Decision Support and Analysis Team
Office of Program and Strategic Analysis (OPSA)
Center for Drug Evaluation and Research (CDER)
U.S. Food and Drug Administration (FDA)
Sara.Eggers@fda.hhs.gov

Public Meeting: Characterizing FDA's Approach to Benefit-Risk Assessment Through the Medical Product Lifecycle

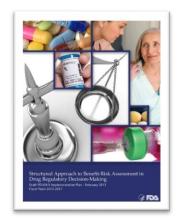
Duke-Margolis Center for Health Policy May 16, 2019



The views and opinions expressed in this presentation are those of the individual presenter and should not be attributed to or considered binding on the U.S. Food and Drug Administration (FDA).

Background on FDA Benefit-Risk Assessment for Human Drug Review





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

PDUFA V* Implementation Plan February 2013

Relevant reading: Sections 1 and 2 https://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM329758.pdf



"Benefit-Risk Assessment in Drug Regulatory Decision-Making"

PDUFA VI** Implementation Plan March 2018

https://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM602885.pdf

FDA 2019 Discussion Document on Benefit-Risk Throughout the Drug Lifecycle¹





Benefit-Risk Assessment Throughout the Drug Lifecycle: FDA Discussion Document

The information contained in this document is for discussion purposes only and should not be interpreted as advice, guidance, or statements on policy from the U.S. Food and Drug Administration (FDA).

Introduction

In accordance with commitments established in the sixth authorization of the Prescription Drug User Fee Act (PDIE4 N) in 2017. *He EPA Intends to publish draft guidance in 2020 on benefit: *disk assessment for new drugs and biologics (referred to collectively in this document as drugs). The planner guidance will articulate the approach of FDA's Center for Drug Evaluation and Research (CDER) and FDA's Center for Biologics Evaluation and Research (CBER) to conducting the benefit: *risk assessments that guide drug regulatory decision-making.* It will discuss opportunities for FDA and sponsors to effectively discuss benefit: *disk considerations throughout the drug development lifecycle. It will also discuss how benefit: *sik information may effectively be communicated to the public. To meet requirements established in the 21" Century Cures Act, *the planned guidance will also discuss how relevant patient experience data may be used to inform benefit: *risk assessments. Further information on FDA's commitments are found in the 2018 PDUFA V implementation plan entitled "Benefit: Risk Assessment in Drug Regulatory Decision-Making."

The intent of the planned benefit-risk guidance is to provide drug sponsors and other stakeholders with better clarity about how considerations about a drug's benefits, risks, and risk management factor into FDA's regulatory decisions about its marketing authorization. Industry stakeholders have indicated that having a clearer understanding of FDA's assessments can help inform sponsors' decisions about their drug development programs and the evidence they generate in support of their new drug application (NDA) or biologics license application (RUA). It may also help patients and other stakeholders gain further insight into the regulatory framing of drug development and evaluation.

On May 16, 2019, the Duke-Margolis Center for Health Policy will convene a public meeting, on behalf of FDA, entitled "Characterizing FDA's Approach to Benefit-Risk Assessment Throughout the Medical Product Life Cycle." The stakeholder input obtained from this meeting will inform development of the draft guidance. Information on the public meeting is found at healthpolicy.duke.edu/events. The public sencouraged to contribute input through participation at the meeting and through the public docket.*

- Pertains to CBER and CDER
 - CDRH has guidance on benefit-risk determinations for medical devices²
- Provides background on FDA's approach to benefit-risk assessment for regulatory decisions regarding marketing authorization
- Identifies topics that FDA may address in draft guidance
- Should not be interpreted as advice, guidance or statements on policy from FDA
- 1. https://healthpolicy.duke.edu/sites/default/files/atoms/files/discussion guide b-r assessment may16.pdf
- 2. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/factors-consider-when-making-benefit-risk-determinations-medical-device-premarket-approval-and-de

What is benefit-risk assessment in human drug review?





Evaluation of the demonstrated benefits and risks of a medical product, and

Making a judgment as to whether the expected benefits outweigh the potential risks associated with its expected use

Fundamental elements of Benefit-Risk Assessment



Decision Context

- Regulatory mission and mandate; Risk management goals
- Product, condition, patient population, constraints, precedents

Options

Expectations (Outcomes)

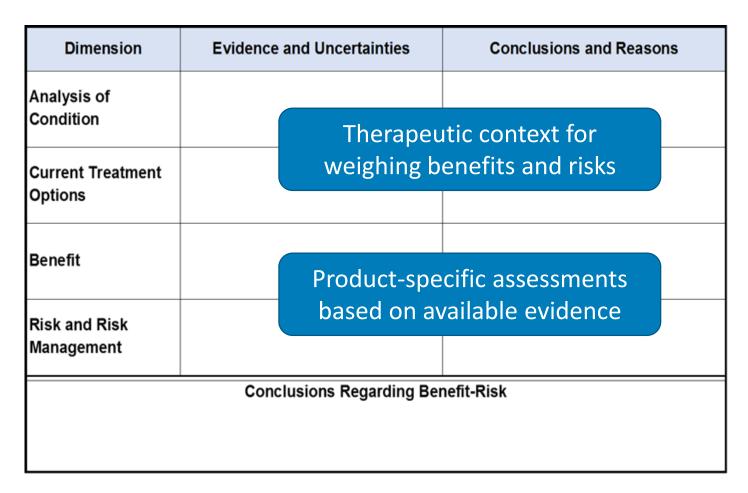
Values

Uncertainty

FDA's Benefit-Risk Framework for Human Drug Review



- Structured approach for B-R assessment and communication
- Implemented into new drug review Satisfying 2012 PDUFA* commitment and FDASIA** requirement
- Reflects reality: B-R assessment is fundamentally a qualitative exercise
- Flexible to include supporting quantitative analyses



Desired outcomes of the Benefit-Risk Framework





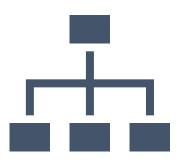


- Sharpen focus on the most relevant issues
- Articulate the applied clinical reasoning and judgment
- Faithfully capture deliberations



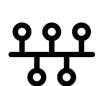
Consistent and accessible

- Improve transparency in the decision-making process
- Provide standard structure for communication
- Provide an accessible record of the decision for reference



Aligned with review process

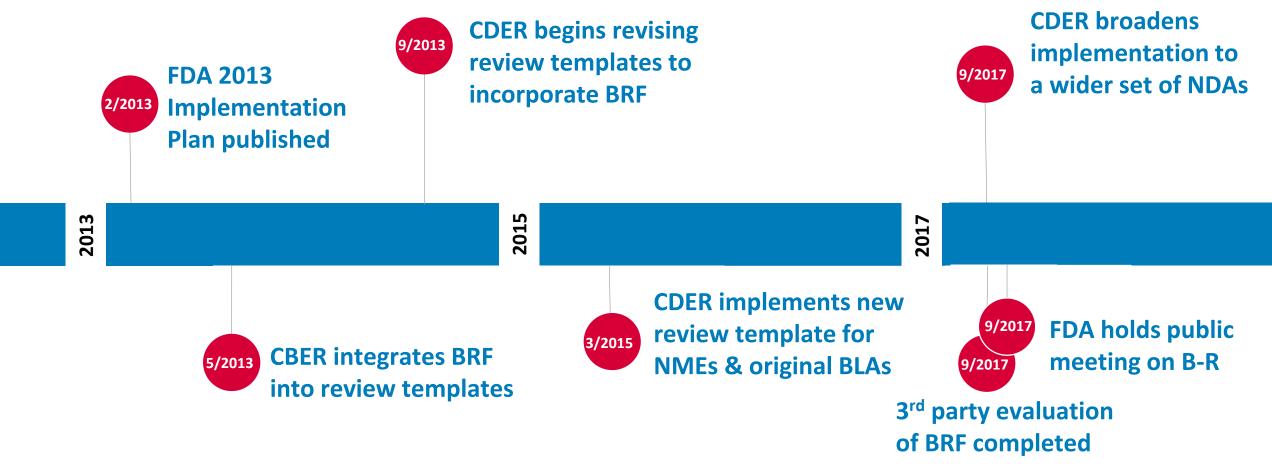
- Fit naturally within existing review processes
- Apply broadly to the range and lifecycle of regulatory decisions



Implementation of the Benefit-Risk Framework



PDUFA V (FY13 - FY18)



Frameworks are available in posted reviews





Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	The US Centers for Disease Control and Prevention estimates that greater than 1.1 million people in the US are living with HIV. Many of these people can achieve virologic suppression and immunologic recovery with an ART regimen comprised of currently approved drugs. However, there is a rare subset of HIV-infected patients who cannot achieve virologic suppression due to the presence of MDR HIV.	Heavily treatment experienced patients with MDR HIV and evidence of ongoing HIV replication despite ART are at high risk of AIDS-related morbidity and mortality.
Current Treatment Options	For patients with MDR HIV infection, providers must individually tailor combination treatment regimens based on previous ART exposure, viral resistance testing, pharmacogenomics, drug tolerability, and co-morbid conditions. The resulting antiretroviral regimens are often burdensome, less well tolerated, and associated with inadequate HIV viral suppression.	Heavily treatment experienced patients with MDR HIV infection need new and effective antiretroviral products that lack cross-resistance with commercially available products.
Benefit	A reduction in HIV RNA ≥ 0.5 log ₁₀ is associated with reduction in disease progression. The pivotal trial, TMB-301, demonstrated a significantly higher percentage of subjects achieving a ≥ 0.5 log ₁₀ decrease in HIV viral load after completion of the Essential Monotherapy Period compared with the percentage of subjects achieving a ≥ 0.5 log ₁₀ decrease in HIV viral load after completion of the Control Period. Additionally, both TMB-301 and the 800 mg q 2 week arm of TMB-202 demonstrated similar longer-term rates of virologic suppression. In Trial 301, 43% of subjects had HIV RNA < 50 copies/mL at week 25. In Trial 202, 44% of subjects had HIV RNA < 50 copies/mL at week 24. Apart from the 2000 mg IV loading dose in TMB-301, these were identical treatment regimens in similar patient populations.	Ibalizumab has clearly demonstrated virologic activity in heavily treatment experienced patients infected with MDR HIV. As TMB-301 was an uncontrolled trial, there remains some uncertainty surrounding the contribution of ibalizumab to the maintenance of virologic suppression. However, the similarity of the Week 25 and Week 24 virologic outcomes in Trials 301 and 202, respectively, may reflect ibalizumab's contribution to longer-term durability.
Risk	Based on the data submitted in support of this BLA, ibalizumab has a favorable safety profile. The nature and frequency of the significant safety events (deaths, SAEs, and discontinuations due to AEs) reported in the BLA largely reflect the patient population targeted for enrollment, i.e., advanced HIV/AIDS patients infected with MDR HIV and failing current ART.	Based on the available data, ibalizumab has a favorable safety profile. The safety database, albeit limited for the proposed dosing regimen, was sufficient for the assessment of safety for the rare population for which this drug will be indicated.
Risk Management	Ibalizumab has a favorable safety profile.	Safety risks have not been identified that require risk management beyond standard pharmacovigilance.

Currently, approval documentation may include more than one BRF

- Some teams complete a BRF at every level of clinical review
- Others have a single BRF completed collaboratively

^{*}for more info, see 2018 Implementation Plan

We have received positive feedback ...



External organization completed evaluation in Sept 2017

Reviewed documentation for 43 applications

Interviewed >300 stakeholders:

- FDA review staff and signatories
- Drug Applicants
- Patients and healthcare providers

Most FDA staff believed the BRF has value in organizing thinking and documenting concise view of review

External stakeholders largely felt that BRFs are

- Effective at communicating reasoning behind FDA's regulatory decision
- Clear and understandable to motivated readers who have some background
- Useful to inform their own decision making (e.g., developing, prescribing, using therapies)

... and suggestions for improvement



External organization completed evaluation in Sept 2017

Reviewed documentation for 43 applications

Interviewed >300 stakeholders:

- FDA review staff and signatories
- Drug Applicants



Stakeholders offered insightful suggestions:

- Improve presentation of content and consistency among BRFs
- Expand use of BRFs to more applications
- Enhance incorporation of patient perspectives, clinical considerations, and quantitative B-R assessments
- Make it easier for stakeholders to find and access BRFs

International Council on Harmonisation (ICH)

FDA

Guidelines for sponsor's submissions

- In 2016, ICH¹ published updated guidelines (M4E(R2)) on Section 2.5.6 "Benefits and Risks Conclusions" in the Common Technical Document
 - To date, there was limited guidance to aid industry in structuring their benefitrisk assessment
 - Regulators were seeing variable approaches taken by applicants

• In July 2017, FDA² revised its *CTD-Efficacy Guidance to Industry* to incorporate the M4E(R2) guidelines to applicants

International Council on Harmonization (ICH)

FDA

M4E(R2) aligns with FDA's Benefit-Risk Framework

Dimension	Evidence and Uncertainties	Conclusions and Reasons	
Analysis of Condition			
Current Treatment Options			
Benefit			
Risk and Risk Management			
	Conclusions Regarding Ber	nefit-Risk	

Revised M4E(R2)

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

FDA committed to continuing the effort



PDUFA VI commitments on Benefit-Risk



Publish updated plan for continued implementation of structured benefitrisk assessment



Conduct a public meeting to gain stakeholder input



Publish draft guidance on FDA's approach to B-R assessment



Conduct a 2nd evaluation of the Benefit-Risk Framework implementation

Additional opportunities to enhance B-R assessment





Make BRFs more easily accessible on FDA's website



Use BRFs to support product-specific discussions at Advisory Committee meetings



Explore use of more structured, quantitative benefit-risk assessment approaches within the qualitative framework, in cases where they provide unique value



In most cases, FDA's benefit-risk assessments are adequately addressed through the qualitative Benefit-Risk Framework

Including additional analytical approaches may provide value in certain cases



Decisions Challenged By:

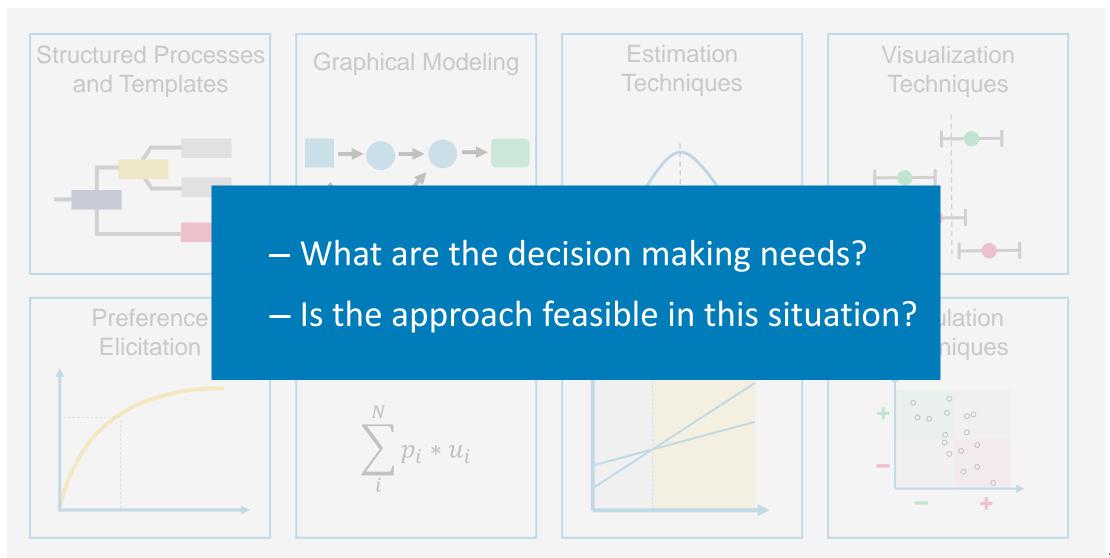
- Novel uncertainties about benefits or risks
- Lack of clear precedent as to how to approach the benefit-risk assessment

Example Situations:

- Pre-market review of rare disease indication
- A therapy that introduces novel safety or product quality issues
- Post-market decision that could lead to unexpected impacts on the healthcare system

There is a suite of potential supporting approaches





Benefit-Risk Assessment must be fit-for-purpose



- It must fit within FDA's regulatory context
 - Our mission is to protect and promote public health
 - We are bound to our laws
 - Our decisions set precedent
- It must fit within FDA's processes
 - There are hundreds of regulatory decisions every year, most are time-sensitive
 - Decision making involves large multi-disciplinary teams of experts
 - Reviews are conducted within a highly structured set of policies, procedures, and templates

Introduction: FDA's approach to Benefit-Risk Assessment

Sara Eggers, PhD & Kerry Jo Lee, MD, U.S. Food & Drug Administration 9:15 am – 10:00 am

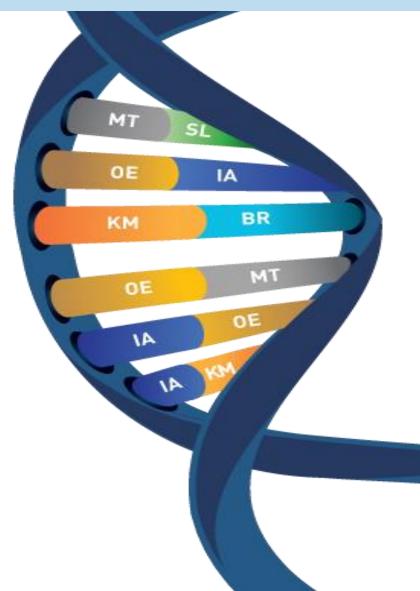




A Perspective on Benefit-Risk and the Regulatory Pathway: The Big Picture

Kerry Jo Lee, M.D.

Office of New Drugs
Center for Drug Evaluation and Research
U.S. Food and Drug Administration





Disclosure

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

"Effective" is codified in statute:

 Demonstrates "substantial evidence that the drug will have the effect it purports or is represented to have under proposed labeled conditions of use"

(21CFR314.125, 21CFR314.126)

 A drug's "effect" forms the basis of its translation to meaningful clinical benefit

"Safe" can be interpreted as the determination that a drug's benefits outweigh its risks for drug's intended use

 Safety is considered in relation to the condition treated, the efficacy purported, and ability to mitigate risk

^{**}http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM329758.pdf



^{*}For simplicity, the term "drug" is used in this presentation to mean both drugs and biologics



What is benefit-risk assessment in human drug review?



Evaluation of the demonstrated benefits and risks of a medical product, and

Making a **judgment** as to whether the expected benefits outweigh the potential risks associated with its expected use

From FDA's Patient-Focused Drug Development Glossary, available at https://www.fda.gov/Drugs/DevelopmentApprovalProcess/ucm610317.htm



New Drugs Regulatory Program Modernization



Objectives

Guiding principles for modernizing the new drugs regulatory program

Scientific Leadership

We will grow our scientific expertise and clarify pathways to regulatory approval.

- Expanding the armamentarium to address unmet medical needs is an important part of our public health mission.
- Towards that end, we will proactively collaborate with academic medical scientists and patient/disease advocates, evaluate scientific gaps, and strategically foster drug development.

Integrated Assessment

We will critically, collaboratively and consistently assess whether information in submissions meets statutory and regulatory requirements.

- We will take a new approach to document our assessments, developing a more integrated, cross-disciplinary document to foster collaboration and reduce redundant information.
- Our assessments will be rigorous, risk-based, and clinically relevant; focus on the key issues; and incorporate the patient perspective.

Benefit-Risk Monitoring

We will establish a unified post-market safety surveillance framework.

• To effectively protect the American public, we will systematically monitor the benefits and risks of approved drugs across their lifecycles.

Managing Talent

We will attract, develop, and retain outstanding people.

• We will use 21st Century Cures Act authorities to recruit and retain technical, scientific and professional experts, and eliminate our backlog of vacant positions.

Operational Excellence

We will have a dedicated focus on operational excellence.

- We will enhance our ability to address OND's large volume workload through greater process standardization and better defined roles and responsibilities.
- This will improve operational efficiency and enable our scientists to focus on science, not ancillary tasks.

Knowledge Management

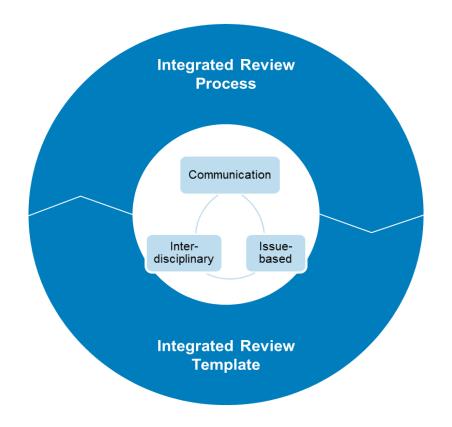
We will facilitate knowledge management.

- Vast and diverse information is submitted to and generated by the New Drugs Regulatory Program.
- We will make it easy for our staff to find and use scientific and regulatory precedents.
- This will reduce manual work time, increase the speed and efficiency of submission assessment, and increase the consistency and predictability of regulatory decision-making.



New Integrated Review for Marketing Applications





Designing an efficient, issue-based interdisciplinary review process and template that results in an integrated FDA assessment of marketing applications and the key issues

Key issues are generally comprised of issues that inform or characterize our **assessment of benefit and risk**.







Creates a template and a process that are issue-based, foster interdisciplinary collaboration, reduce redundancy and low-value work, and enable better knowledge management

 Facilitates interdisciplinary assessment and communication on issues of benefit and risk

Develops a tracking tool to be utilized from pre-NDA through end of review cycle, allowing for systematic tracking of review issues for the entire review team

 Enables interdisciplinary transparency and collaboration on issues relevant to the assessment of benefit and risk

Adds new roles: (1) Clinical Data Scientists to support safety analysis and (2) Medical Editors to provide editing and formatting services

 Allows more time for reviewers and review teams to focus on the critical thought and analyses that inform benefit and risk issues and assessments

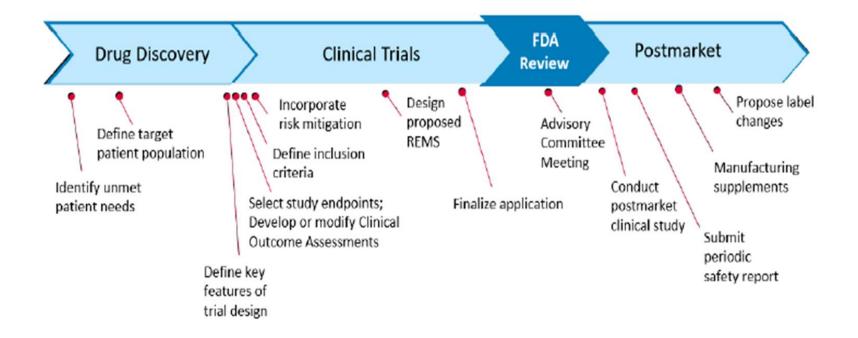
Incorporates purposeful scoping meetings with early involvement of leadership to discuss benefit and risk issues; and joint assessment meetings focused on specific review issues

 Focuses discussion on the key issues related to benefit and risk early and often throughout the review



The Drug Development Life-Cycle and Benefit-Risk: The 360° View





Sample milestones along the drug lifecycle that may have a particular bearing on benefit-risk assessment of a marketing authorization. Milestones may not apply to all drug development programs.

From Benefit-Risk Assessment Throughout the Drug Lifecycle: FDA Discussion Document, page 6



Introduction: FDA's approach to Benefit-Risk Assessment

Sara Eggers, PhD & Kerry Jo Lee, MD, U.S. Food & Drug Administration 9:15 am – 10:00 am



Break

10:00 am - 10:15 am



Session 1: Activities that Occur in Pre-Market Development that Best Inform FDA's Benefit-Risk Assessment

10:15 am - 12:00 pm



Session 1: Presentation

James Smith, MD, MS, U.S. Food & Drug Administration





Key Considerations into FDA's Benefit-Risk Assessment of a Pre-Marketing Application

James P. Smith, MD, MS

Office of New Drugs
Center for Drug Evaluation and Research
U.S. Food and Drug Administration



Disclosure

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Analysis of Condition

Current Treatment Options

Benefit

Risk & Risk Management



Benefit-Risk Assessment



Benefit-Risk Conclusion



Benefit-Risk Assessment

- Benefit-risk assessment requires forming judgment
- Judgment is informed by integrating many different "inputs"
- Inputs are supported by the available evidence and analyses
- Some degree of uncertainty about the inputs always exists
- Our judgment must take these uncertainties into account

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Analysis of Condition

- Context of use for the proposed indication
 - How is patient population defined? Are there known subsets with particular unmet needs?
- Clinical aspects of the condition
 - Prevalence? Severity? Natural history? Heterogeneity of disease?
 Impact on quality of life?
- Patient-focused disease burden
- Influence on trial designs, patient selection, dose selection, duration of trials, endpoints, tolerance for risks, and more



Current Treatment Options

- Goals of current standard of care
- Efficacy & safety of available therapies (including in specific subsets, if data are available)
- Burden of current treatments (including tolerability)
- Does new therapy fill a gap? Provide an alternative? Patient perspectives on unmet needs?
- Influence trial design (e.g., add-on vs. alternative; consider active control?), patient selection, endpoints



Benefit

- Strengths/limitations of clinical trial(s) & implications for assessing efficacy
 - Design, size, or number of trials are not determinative
- Clinical relevance of study endpoints (includes surrogate endpoints)
- Clinical significance of demonstrated results, including patient perspective if available
 - Nature of benefit (magnitude, duration, outcomes)
 - Ability for patients/providers to distinguish individual benefits
 - Ability to predict which patients may benefit (and magnitude)
- Anticipated benefit in the post-market setting
- During development, anticipated risks could inform choice of endpoints to characterize benefit; obtain patient perspective early



Risk & Risk Management

- Strengths/limitations of the safety evaluation have implications for assessing drug risks
 - # exposed, duration, design (controlled vs. single-arm), background rate of adverse event in the treated population
- Clinical significance of safety observations, including patient perspective if available
 - Nature of harm (including severity, expected onset/duration, reversibility)
 - Ability to predict, prevent, detect, and mitigate harms
- Uncertainty is expected
 - Trials are generally not powered for safety outcomes: absence of evidence ≠ evidence of absence
 - Underrepresentation of at-risk populations in clinical trials
 - Quantitative relationships often unknown between "signals" and adverse outcomes
- Anticipated risks in the post-market setting how will real-world use differ than trials (e.g., patient selection, monitoring, availability of labeling, risk management strategies)?
- Consider: what uncertainties could be reduced during late-stage development?



Putting it Together: Benefit-Risk Conclusion

- Weighing benefit-risk must consider product-specific data in a therapeutic context
 - Tolerance for uncertainty and trade-offs about a product's benefit & risk vary with clinical situation. Patient perspective can inform this consideration.
- A judgment is made regarding whether the probability (and magnitude) of benefit seems to exceed the probability (and magnitude) of harm
 - Labeling (or other measures) may increase the likelihood of benefit and reduce the likelihood of harm
- What further evidence may be necessary to address uncertainties related to benefits (e.g., accelerated approvals) or harms?
- Supplementary quantitative approaches may be informative to the overall qualitative benefit-risk assessment



Summary

- Analysis of condition, current treatment options, expected benefits, and expected risks/risk management are the "inputs" into FDA's benefit-risk assessment during review of a marketing application.
- Although described and discussed individually in the benefit-risk framework, the ultimate conclusion follows from the interaction of these elements.
- Considering the benefit-risk framework early can influence a development program, such as the intended use of the drug, patient selection, trial designs, endpoints, and investigation of risk mitigation strategies.



Session 1: Panel Discussion

Activities that Occur in Pre-Market Development that Best Inform FDA's Benefit-Risk Assessment



Quant. Safety & Epidemiology

Public Meeting: Characterizing FDA's Approach to **Benefit-Risk Assessment throughout the Medical Product Life Cycle**

Activities in pre-market development informing benefit-risk Conny Berlin Global Head Quantitative Safety & Epidemiology, Novartis **Industry Lead IMI PREFER** 16 May 2019

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Structured benefit-risk approach Novartis achievements

- Key benefits and key risks are selected and why.
- Which comparators were chosen.
- The magnitude of benefit and risk effects.
- Presentation in a graphical/tabular summary together with concise text.
- Written in such a way that it allows a dialogue with all stakeholders.



Pre-market development activities that best inform FDA's b-r assessment

- Understanding the patient perspective
- Benefit-risk assessment in the context of the treatment landscape



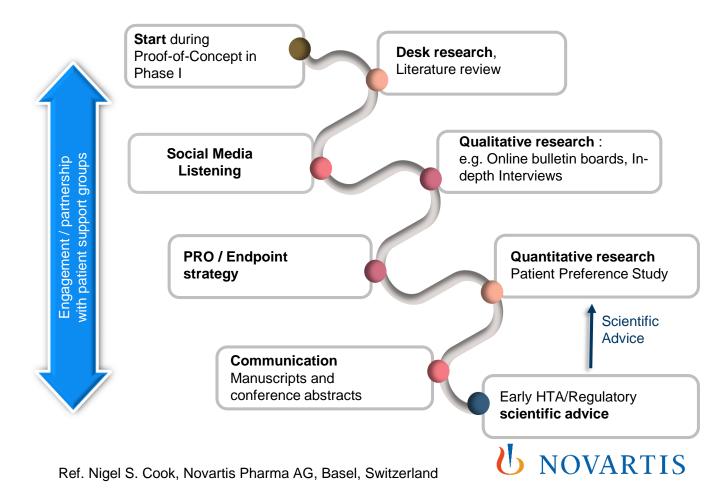
Understanding the patient perspective

Key considerations in FDA's benefit-risk framework

«Benefit», «Risk and Risk Management», «Conclusions regarding benefit-risk»

- Clinical relevance of the study endpoints: ability to measure or predict clinical outcomes of importance to patients
- Demonstrated results and their clinical significance, informed by:
 - Patient perspectives on benefit
- Serious adverse events or safety signals clinical significance and remaining uncertainties, considering:
 - Patient perspectives on risks
- Benefit and risk values and tradeoffs, including patient perspectives

What should the sponsor consider when generating evidence?



Understanding the patient perspective

What FDA guidance or other resources should be consulted?

By developing expert and evidence-based recommendations, PREFER aims to guide industry, regulatory authorities and HTA bodies and reimbursement agencies on how patient preferences can be assessed and used to inform medical product <u>decision making</u>.



5 year project: 2016 - 2021



Benefit-risk assessment in the context of the treatment landscape

Key considerations in FDA's benefit- risk framework

«Current treatment options»

- Efficacy and safety of available therapies
- Aspects of disease burden not addressed by current therapies

«Conclusions regarding benefit-risk»

 How does the product, if approved, may enhance the treatment landscape?

What should the sponsor consider when generating evidence?

Based on current treatment options

- Early definition of key benefits and risks
- What is the magnitude of the effects of the available therapies?
- What are the strengths and limitations of the trial designs of comparator programs?

Design development program

Consider current treatment options as comparators for development studies

Benefit-risk assessment

- How will the benefit and risk effects of the investigational product compare to other therapies in the development program? 1)
- How will the benefit and risk effects of the investigational product compare to published evidence of other available therapies? 1)
- Apply best practice statistical methods; consider strengths and limitations of the trial designs
- Provide tabular or graphical summaries



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Thank you



About the PREFER project







The Patient Preferences in Benefit-Risk Assessments during the Drug Life Cycle (PREFER) is a five year project that has received funding from the **Innovative Medicines Initiative** 2 Joint Undertaking under grant agreement No 115966. This Joint Undertaking receives support from the European Union's **Horizon 2020** research and innovation programme and **EFPIA**.



Session 1: Panel Discussion

Activities that Occur in Pre-Market Development that Best Inform FDA's Benefit-Risk Assessment





16 May 2019

Activities that Occur in Pre-Market Development that Best Inform FDA's Benefit-Risk Assessment

Benefit-Risk Assessment Throughout the Drug Lifecycle

Brett Hauber, PhD

Senior Economist and Vice President Health Preference Assessment RTI Health Solutions Affiliate Associate Professor
CHOICE Institute
University of Washington School of Pharmacy

The power of knowledge. The value of understanding.

Patient Preference Information



Definition¹

...qualitative or quantitative assessments of the relative desirability or acceptability to patients of specified alternatives or choices among outcomes or other attributes that differ among alternative health interventions

Three Types of Patient Preference Information²

Attributes	What matters	
		Priorities
Relative Importance	How much it matters	
Tradeoffs	What tradeoffs patients are willing to make	Preferences

Each of the three types of patient preference information can provide useful information throughout FDA's Benefit-Risk Framework

¹ CDRH Guidance https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM446680.pdf
2 MDIC Benefit-Risk Guidance: https://mdic.org/wp-content/uploads/2018/05/MDIC PCBR Framework Web.pdf

Patient Preferences in Medical Product Development



Types of Patient Preference Information Potentially Useful to FDA

Development	Clinical Trial Design	Pre-market Benefit- Risk Assessment	Postmarket
 Identify unmet medical need Understand what matters most to patients about their disease or treatment 	 Inform endpoint selection Inform performance goal 	 Analysis of condition Current treatment options Patients' perspective on benefit-risk tradeoffs 	 Inform interpretation of new data affecting benefit-risk assessment Communicate benefit-risk information to patients

FDA has identified multiple potential uses of patient preference information that can be applied to FDA's Benefit-Risk Framework

FDA/CERSI PPI Workshop, December 7, 2017. https://pharm.ucsf.edu/sites/pharm.ucsf.edu/files/cersi/media-browser/Annie%20Saha%20Million%20Tegenge.pdf

Key Considerations in FDA's Benefit-Risk Framework



Where patient preference information may inform key considerations

Dimension	Evidence and Uncertainties	Conclusions and Reasons		
Analysis of Condition	Patient input on disease burden			
Current Treatment Options	Patient input on unmet medical need			
Benefit	Patient perspective on benefit			
Risk and Risk Management	Patient perspective on risk			
Conclusions Regarding Benefit-Risk				
Benefit-risk tradeoffs Importance of unresolved uncertainties				

FDA 2018. Benefit-Risk Assessment in Drug Regulatory Decision Making https://www.fda.gov/media/112570/download

How Patient Preference Information Might be Used



Therapeutic Context

Key Consideration	What Patient Preference Can Offer
Patient input on disease burden	 Importance of reducing specific disease impacts Willingness to accept (i.e., trade off) risks to reduce disease impacts
Patient input on unmet medical need	 Importance of incremental improvements relative to available treatments Willingness to accept (i.e., trade off) additional risks for improvements beyond what is currently available Willingness to forego benefits to avoid risks of what is currently available

How Patient Preference Information Might be Used



Clinical Outcomes

Key Consideration	What Patient Preference Can Offer
Patient perspective on benefit	 Clinical meaningfulness Endpoint selection Does the treatment address what matters? Does the treatment address what matters most? Performance goal What is the minimum benefit (effect size) required given the level of risk?
Patient perspective on risk	 Risk tolerance Which risks are most bothersome or concerning? What is the maximum level of risk the is acceptable given the level of benefit

How Patient Preference Information Might be Used



Benefit-Risk Balance

Key Consideration	What Patient Preference Can Offer
Benefit-Risk tradeoffs	 Do patients perceive the benefits of a therapy (as demonstrated in clinical studies) to outweigh known or potential risks? Does a subset of patients perceive the benefits to outweigh the risks?
Importance of unresolved uncertainties	 What level of uncertainty in benefits are patients willing to accept? What level of uncertainty in risks are patients willing to accept?

Conclusions



- ✓ Patient preference information can be useful in each section of FDA's Benefit-Risk Framework
 - ✓ Not just in looking at the overall benefit-risk balance
- ✓ There are many examples of patient preference studies that provide each type of information.
- The key will be to determine
 - ✓ What specific patient preference information is most useful to FDA and drug developers.
 - ✓ What are the standards that will be used to establish the credibility of patient preference information for these purposes

Session 1: Panel Discussion

Activities that Occur in Pre-Market Development that Best Inform FDA's Benefit-Risk Assessment



Session 1: Activities that Occur in Pre-Market Development that Best Inform FDA's Benefit-Risk Assessment

10:15 am - 12:00 pm



Lunch

12:00 pm - 1:00 pm



Session 2: Effectively Communicating Benefit-Risk Assessment Information

1:00 pm - 2:15 pm



Session 2: Presentation

Richard Forshee, PhD, U.S. Food & Drug Administration





Benefit-Risk Assessment at CBER

Richard Forshee, PhD

Analytics and Benefit-Risk Assessment Team
Office of Biostatistics and Epidemiology (OBE)
Center for Biologics Evaluation and Research (CBER)
U.S. Food and Drug Administration (FDA)
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Public Meeting: Characterizing FDA's Approach to Benefit-Risk Assessment Through the Medical Product Lifecycle

Duke-Margolis Center for Health Policy May 16, 2019

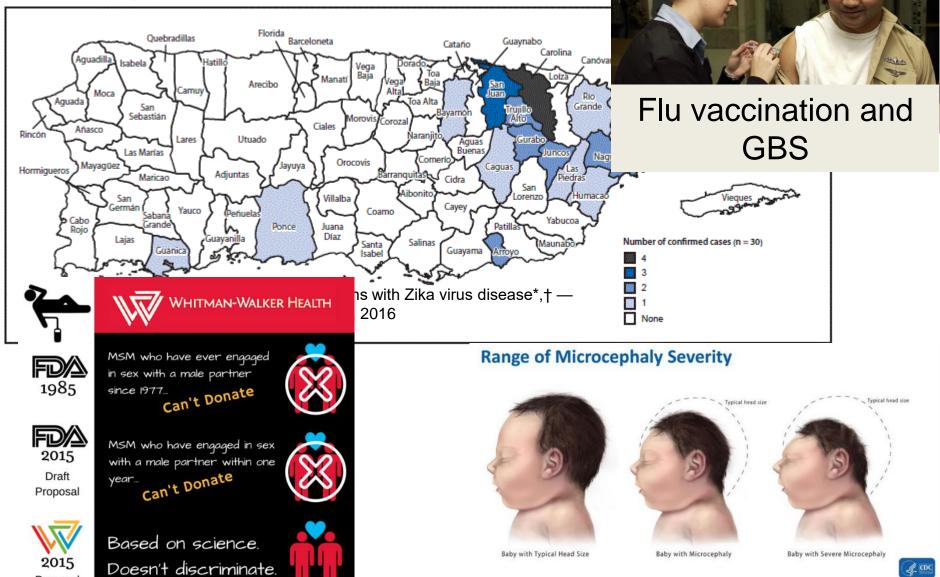
Proposal

Zika infections increasing rapidly in Puerto Rico

Widespread Zika infections warrant urgent action to protect pregnant women









B-R Model for Home-Use HIV Test Kit



Purpose of Model

- The model is a tool to estimate the public health benefits and risks of the OraQuick® In-Home HIV Test kit based on its performance in Phase III trials.
- It helps to integrate many sources of data and explore how different assumptions would affect the estimates of public health benefits and risks.

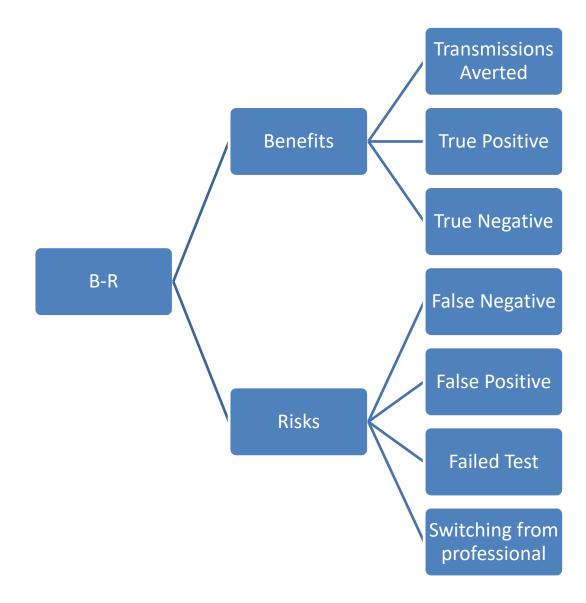


Purpose of the Model (continued)

- Benefits and risks explored in the model are not directly comparable, so professional judgment is required.
- We believe the model helped decision-makers make informed judgments about the likely public health implications of this product.

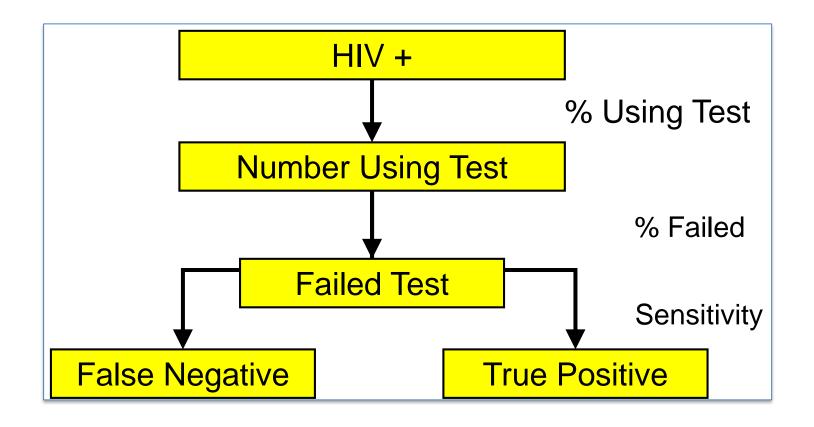
Value Tree for HIV Test Kit





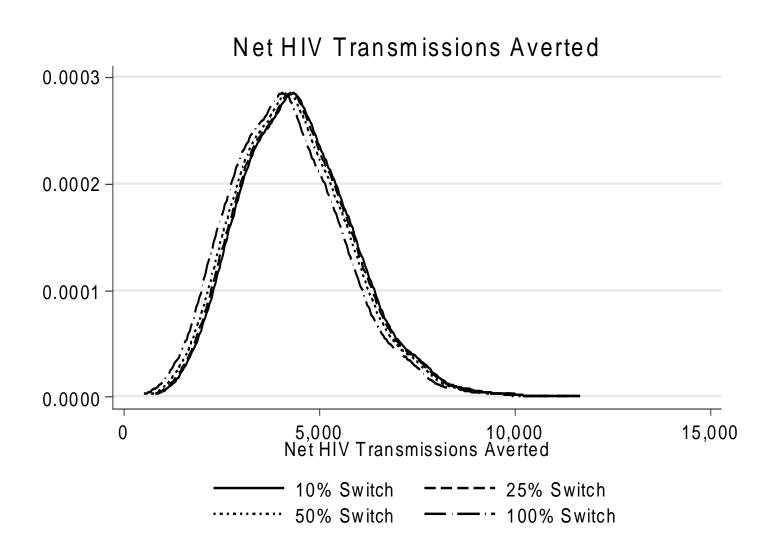
Flow Charts or Influence Diagrams





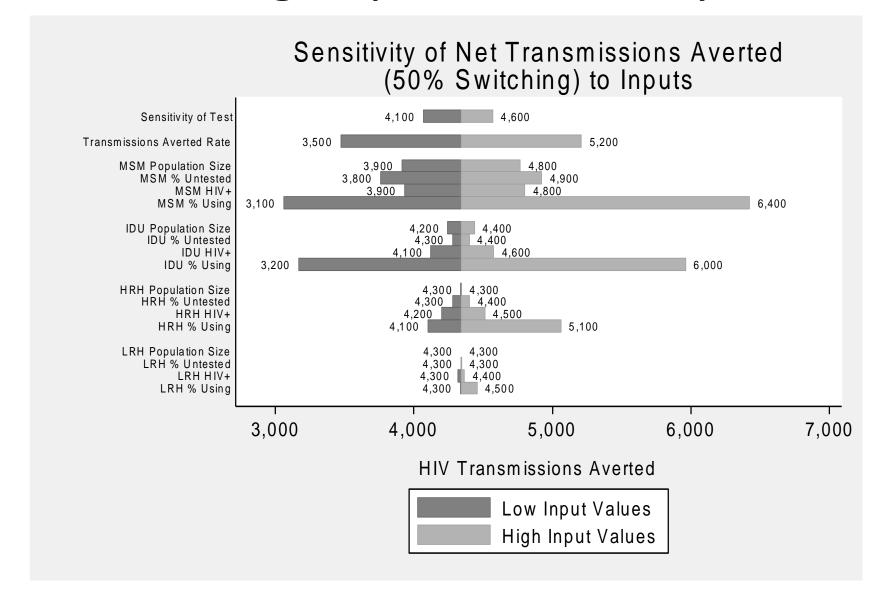


Showing distributions of outputs





Conducting Importance Analyses





Home-Use HIV Test Kit Team

Center for Biologics Evaluation and Research (CBER), FDA

Mark Walderhaug
Estelle Russek-Cohen
Hong Yang
Arianna Simonetti
Elliot Cowan
Hilary Hoffman
Jay Epstein

Centers for Disease Control and Prevention (CDC)

Bernard Branson Arielle Lasry Stephanie Sansom





CBER Team



Session 2: Presentation

Ellis Unger, MD, U.S. Food & Drug Administration







Public Meeting: Characterizing FDA's Approach to Benefit-Risk Assessment throughout the Medical Product Life Cycle

Duke-Margolis Center for Health Policy May 16, 2019

Ellis Unger, MD

Director

Office of Drug Evaluation-I

Office of New Drugs

Center for Drug Evaluation and Research (CDER)

U.S. Food and Drug Administration (FDA)

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Communicating Benefit-risk Information



- Absolute vs. relative effects
- Putting scales into perspective
- Responder analyses
- Histograms
- Forest plots

Communication of the Benefits and Risks: General Principles



• For benefits:

- It's critically important to put benefits into perspective.
- How would you explain the benefits to a patient who was deciding whether or not to use the drug?

• For risks:

- Risks also need clear, quantitative descriptions.
- What are the risks and their probabilities?
- How can risks be monitored? Mitigated?
- Need to distinguish actual harms from nuisance side effects.

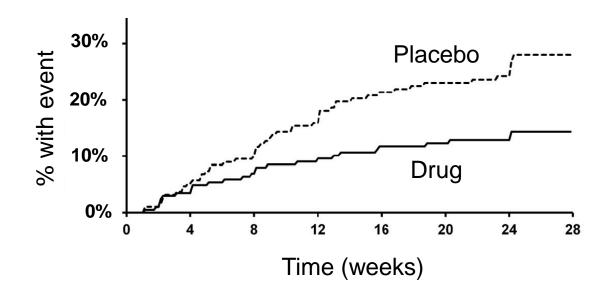
Absolute vs. Relative Risk (1)



- Here the efficacy of the drug is to <u>prevent</u> an adverse consequence
- Patients randomized to drug or placebo
- Primary endpoint is time-to-event

Results:

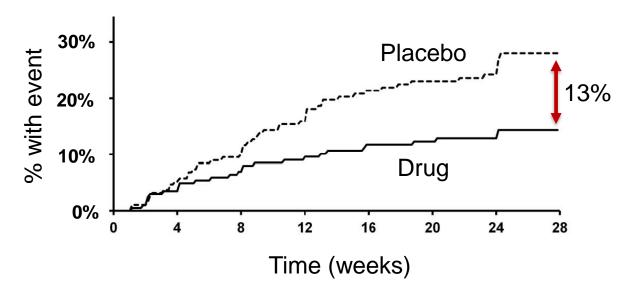
- odds ratio = 0.50 (sometimes the relative risk is calculated)
- p-value = 0.004



Absolute vs. Relative Risk (2)



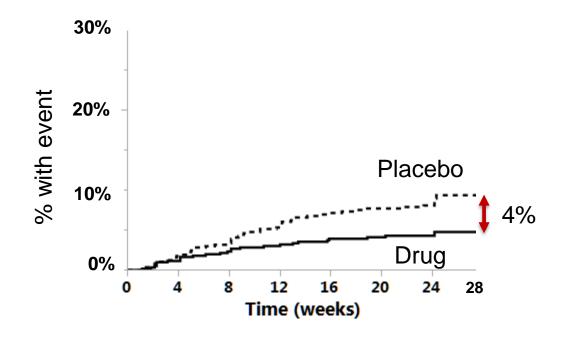
- The relative treatment effect is a 50% reduction.
- The <u>absolute</u> treatment effect is prevention of the event in 13% of individuals at 28 weeks
- Number needed to treat (NNT) = 6 (28 weeks)
- Note: the *p*-value (0.004) does not convey the benefit.



Absolute vs. Relative Risk (3)



- New study. The <u>relative</u> treatment effect is the same: 50%
- But the <u>absolute</u> treatment effect is now only 4%.
- Number needed to treat (NNT) = 25 (28 weeks)
- To understand the benefit, it is critical to express benefit in absolute terms. Expression in relative terms is not very helpful.



Continuous Scales



 Comparison of mean responses to a drug and placebo on a standard scale:

	Baseline	On treatment	Change from baseline		
Placebo	19.1	21.9	2.8		
Drug	19.2	23.9	4.7		

- Treatment effect is 4.7 2.8 = 1.9
- What is missing?
 - What is the range of the scale? 0 to 25? 0 to 100?
 - How meaningful is the 1.9-point treatment effect to patients?

Continuous Scale – Responder Analysis (1)



	Baseline	On treatment	Change from baseline		
Placebo	19.1	21.9	2.8		
Drug	19.2	23.9	4.7		

- Responder analysis: If one can define a "response" at a specific threshold, the percentages of patients with a "response" can be calculated and compared.
- <u>BUT</u> it is imperative to define a "response" and describe its clinical meaning and meaningfulness to patients.

Continuous Scale – Responder Analysis (2)



• If a "response" is defined at ≥ 10 points:

	Baseline	On treatment	Change from baseline		
Placebo	19.1	21.9	2.8		
Drug	19.2	23.9	4.7		

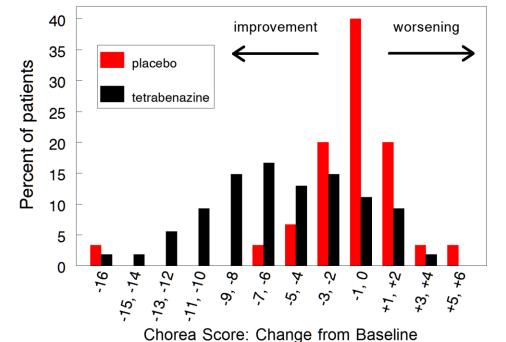
- One can calculate that the numbers of "responders" are 50% and 30% in the drug and placebo groups, respectively.
- The absolute treatment effect is 20%.
- By dichotomizing the scale, information is lost, but results are better expressed for benefit.

Not Everyone Has the Same Response to a Drug – Distribution of Effect



- For benefit, consider that the mean effect size, although important, only represents part of the picture.
- Consider the distribution of results, e.g., % of patients with improvement of at least X; % of patients whose symptoms

resolve.

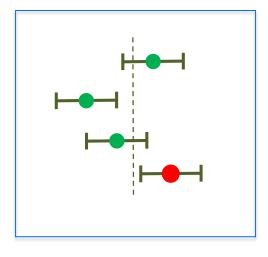




Forest Plots Can be Useful to Convey Benefits and Risks

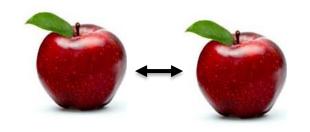
- Comparison of benefits and risks on a common scale is usually difficult, but...
- If benefits and risks comparable, can show them side-by-side
- Forest plot can display the benefit-risk for the overall population as well as for important subgroups.

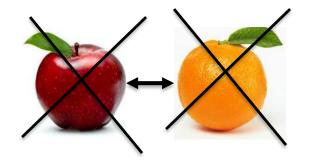
Forest Plot





Try to Compare Apples to Apples





 If you can express benefit as % of patients with benefit of at least X (drug – comparator), try to express risk similarly (% of patients with *important* adverse events)



Vorapaxar: Quantitative Benefit and Risk (in subgroups)

- Anti-platelet drug; approved 2014
- A preventive therapy indicated for the reduction of thrombotic cardiovascular events in patients with a history of heart attack or with peripheral arterial disease.
- Vorapaxar causes bleeding.



Benefit (Left) and Risk (Right) Side-by-side by Subgroup: Percent with CV Death, MI, Stroke, or UCR (Left) Percent with Moderate or Severe Bleeding (Right)

			BENEFIT			RISK					
			Efficacy (MACE +)			Bleeding (GUSTO Moderate or Severe)					
		<u>%</u>	<u>Vorapaxa</u> r	Placebo	Delta	RR	Vorapaxar	Placebo	Delta	RR	ΔΔ%
All		20170	8.9%	10.6%	1.7%	0.84	3.0%	2.0%	-1.0%	1.52	0.7%
Age	<53	26%	7.4%	9.4%	2.1%	0.78	1.3%	0.8%	-0.5%	1.64	1.5%
	53 to <61	27%	7.5%	9.8%	2.3%	0.77	2.2%	1.5%	-0.7%	1.47	1.6%
	61 to <69	25%	8.5%	10.2%	1.8%	0.83	3.3%	2.1%	-1.2%	1.60	0.5%
	>=69	22%	12.8%	13.6%	0.8%	0.94	5.7%	4.0%	-1.7%	1.42	-0.9%
Sex	Male	78%	8.5%	10.2%	1.7%	0.83	2.8%	1.9%	-0.9%	1.48	0.8%
	Female	22%	10.2%	12.1%	1.9%	0.84	3.7%	2.3%	-1.4%	1.61	0.5%
Race	Caucasian	89%	8.6%	10.5%	1.9%	0.82	3.1%	2.0%	-1.1%	1.53	0.8%
	Black	2%	15.6%	15.5%	0.0%	1.00	2.6%	3.4%	0.8%	0.77	0.7%
	Asian	3%	7.8%	7.1%	-0.7%	1.11	2.4%	0.8%	-1.6%	2.84	-2.3%
	Other/unkn	6%	11.1%	13.4%	2.3%	0.83	2.2%	1.6%	-0.7%	1.44	1.6%
Weight	<60 kg	6%	10.7%	8.6%	-2.1%	1.24	5.0%	2.9%	-2.1%	1.71	-4.2%
	<72 kg	24%	9.3%	10.5%	1.2%	0.89	3.4%	2.6%	-0.8%	1.31	0.4%
	72 to <82	25%	8.1%	9.4%	1.2%	0.87	3.4%	2.0%	-1.4%	1.73	-0.2%
	82 to <93.4	26%	8.1%	10.3%	2.2%	0.79	2.6%	1.9%	-0.8%	1.43	1.4%
	>=93.4	25%	10.1%	12.4%	2.3%	0.82	2.6%	1.6%	-1.0%	1.66	1.2%
eGFR	<66.7	23%	13.1%	15.0%	1.9%	0.88	5.3%	3.5%	-1.7%	1.50	0.1%
	66.7 to <79.8	25%	8.5%	9.8%	1.3%	0.86	3.2%	1.7%	-1.5%	1.87	-0.1%
	79.8 to <93.5	25%	7.6%	9.8%	2.2%	0.78	2.1%	1.4%	-0.7%08	1.52	1.5%
	>=93.5	26%	6.8%	8.5%	1.8%	0.79	1.8%	1.5%	-0.3%	1.21	1.5%

Summary



- Benefit-risk assessment is central in what we do.
- B-R assessment requires a thoughtful approach.
- Think in terms of communicating benefits and risks to patients or practitioners.
- In comparing benefits and risks, try to compare apples to apples.
- Histograms, tables, forest plots can be helpful.





Thank you for your attention!

Questions?





Backup Slides



Quantitative Benefit-Risk for Trials with Continuous Endpoints

- It can be difficult to place values on the efficacy and the harms.
- Various patients will value them differently, depending on their symptoms, life experiences, and perceptions.
- Some examples follow...



Gabapentin for Restless Legs Syndrome

- Approved 2011
- Primary endpoint: International Restless Leg Syndrome Rating Scale
- What is a 4.4-point difference worth (range is 0 to 40)?
- It would be important to define a "response" worth having.

	Study		
	HORIZANT		
	1,200 mg	Placebo	
Week 12	(N = 112)	(N = 108)	
Mean Change in IRLS Score	-13.2	-8.8	113



Gabapentin - Restless Legs Syndrome

Safety concerns:

Driving impairment

Somnolence/sedation and dizziness

Suicidal thoughts or behaviors

How does one weigh these concerns against changes in the International RLS Rating Scale? (Answer: not easily!)



Gabapentin - Restless Legs Syndrome

What is the absolute risk of death/injury from impaired driving caused by this drug?

And how does one consider risk to occupants in the car?

And bystanders?

And if the label advises patients not to drive, then how much does that strategy reduce the risk?

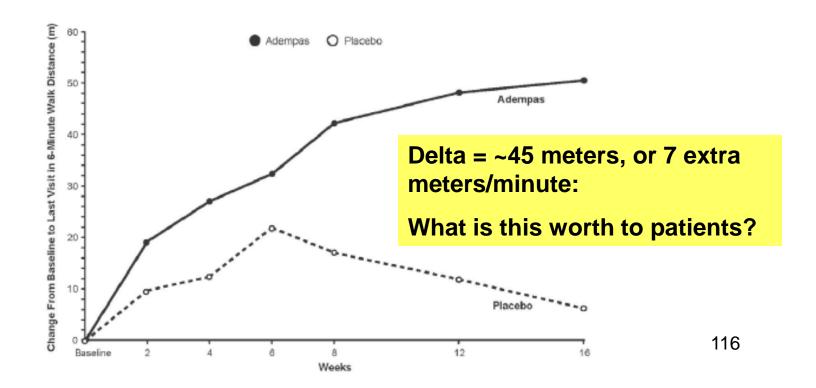
How often can one expect a patient to commit suicide? (It is a class warning – there were no suicides in the development program.)



Riociguat - Pulmonary Hypertension

Approved 2013

Primary endpoint: Change from baseline in 6-minute walk test





Riociguat - Pulmonary Hypertension

Safety concerns:

Hypotension (10% drug; 4% placebo)

Serious bleeding (2.4% drug; 0% placebo)

How does one weigh these harms?

Session 2: Panel Discussion

Effectively Communicating Benefit-Risk Assessment Information



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



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?

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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**?

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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!

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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

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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 Thinking: Integrated Benefit-Risk Science

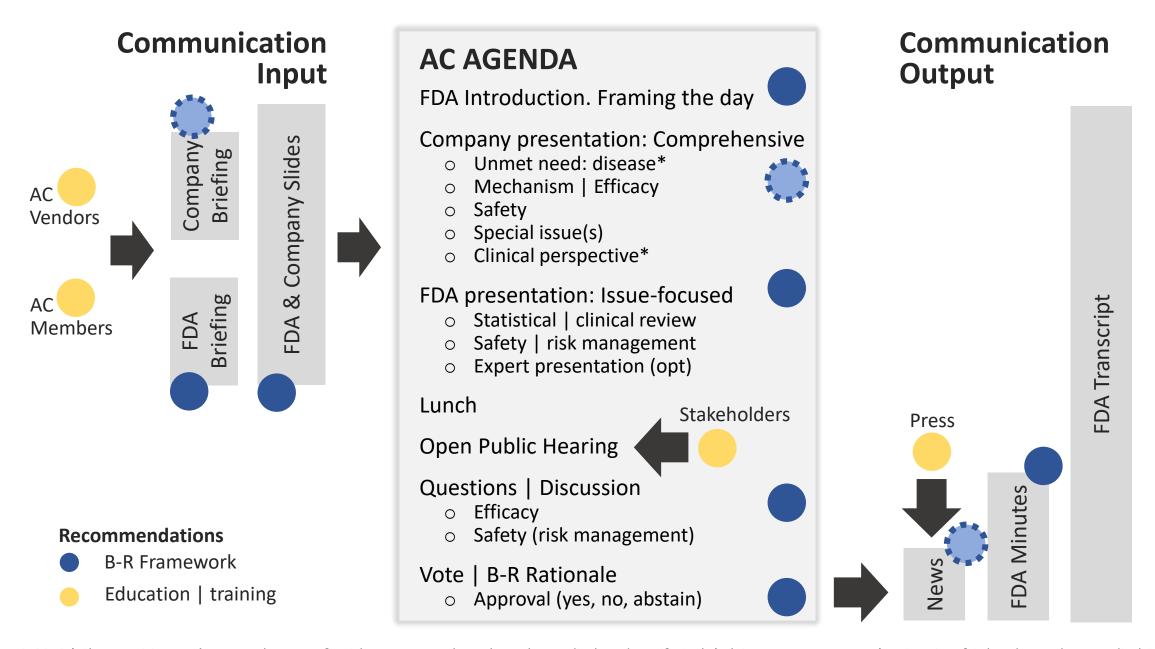
What's Needed Here?: Connection, Collaboration, and Communication

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

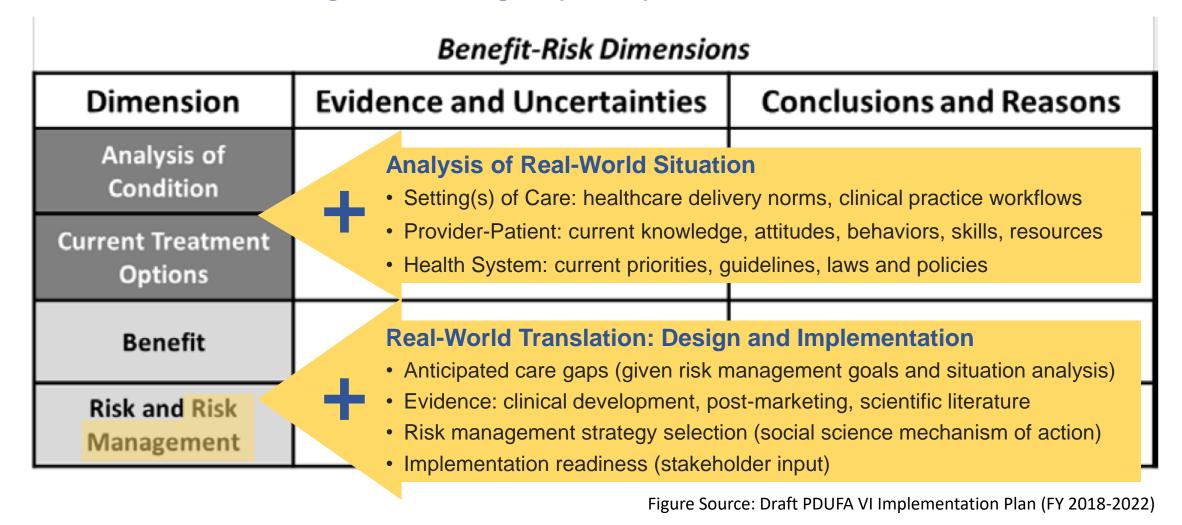
Session 2: Panel Discussion

Effectively Communicating Benefit-Risk Assessment Information





Extending the B-R Framework for AC Discussion and Deliberation on Risk Evaluation and Mitigation Strategies (REMS)



Session 2: Panel Discussion

Effectively Communicating Benefit-Risk Assessment Information



Benefit Risk Assessment: Incorporating the Patient Perspective

Theresa V. Strong, PhD

Director of Research Programs

Foundation for Prader-Willi Research



Prader-Willi Syndrome



- Complex neurodevelopmental disorder caused by loss of paternally expressed, imprinted genes on chr15q11-13
- Frequency ~1/15,000 births: occurs spontaneously, affects males/females, all races and ethnicities
- Major features:
 - Multiple clinical issues: endocrinopathies, scoliosis, gastrointestinal problems, temperature dysregulation, decreased pain sensitivity
 - Hallmark symptoms: Hypotonia, FTT → hyperphagia, obesity
 - Mild to moderate intellectual disability
 - Challenging behavioral profile with high risk of mental illness









International Consortium to Advance Clinical Trials in PWS

www.pwsctc.org

- Multi-stakeholder effort that leverages expertise of patient advocacy groups, industry, and academicians, with input from FDA and EMA
- Address the unmet scientific, technical, clinical and regulatory needs of clinical trials for PWS in the precompetitive space
- Use of rigorous scientific methods
- Patient and caregiver perspective integrated throughout













































International Consortium to Advance Clinical Trials in PWS

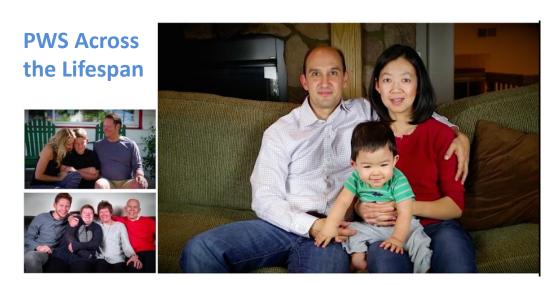
www.pwsctc.org

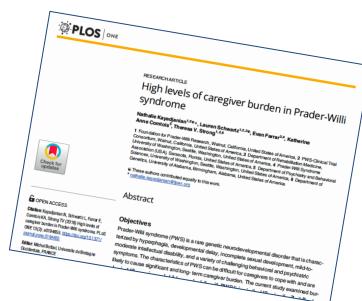
Current areas of focus

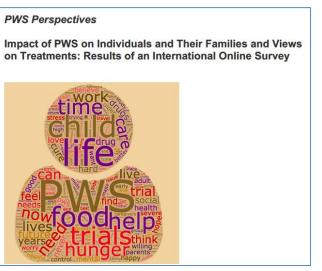
Development of patient-centric endpoints

Convey patient experience to inform product development and regulatory decision making:

- Unmet medical needs
- Impact of PWS on individual and their family







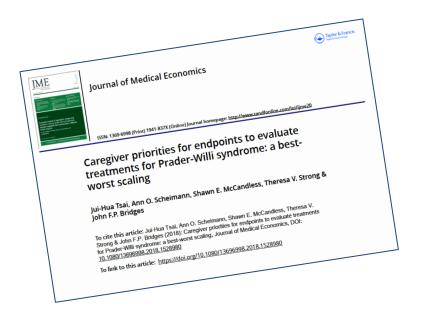


International Consortium to Advance Clinical Trials in PWS

www.pwsctc.org

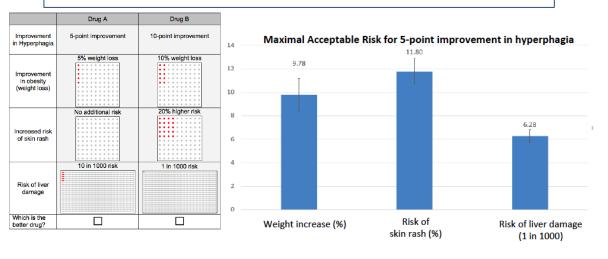
Current areas of focus (cont'd)

- Treatment preferences using quantitative methods
- Risk tolerance
- Meaningful outcomes and improvement in QOL





Treatment Benefit and Risk Tolerance: A Discrete-Choice Experiment Tsai & Bridges, in preparation



Incorporating the Patient Perspective into the Benefit Risk Assessment

- How can the channels for patients/patient groups to contribute to discussions on disease-specific considerations that inform the B/R assessment be strengthened?
- How can sharing of 'product-agnostic' patient experience data be encouraged/incentivized?
- How do we ensure that patient experience information generated by patients/patient groups is reaching those who are making benefit risk assessments and regulatory decisions?



Guidance: Additional clarity on what information is useful; how it is being used and best practices for patients/patient groups to directly convey appropriate information to relevant FDA staff





Session 2: Panel Discussion

Effectively Communicating Benefit-Risk Assessment Information



Session 2: Effectively Communicating Benefit-Risk Assessment Information

1:00 pm - 2:15 pm



Break

2:15 pm - 2:30 pm



Session 3: Using Benefit-Risk Assessment to Inform FDA and Sponsor Decision-Making in the Post-Marketing Setting

2:30 pm - 3:45 pm



Session 3: Presentation

Judith Zander, MD, U.S. Food & Drug Administration





USING BENEFIT-RISK to INFORM FDA and SPONSOR DECISION- MAKING in the POST- MARKETING SETTING

Judith W. Zander, M.D. Director

Office of Pharmacovigilance and Epidemiology Office of Surveillance and Epidemiology Center of Drug Evaluation and Research



The opinions expressed in this lecture are those of the presenter, and do not necessarily represent the views of the US Food and Drug Administration or the US Government

No conflicts of interest to disclose



Agenda

- When might FDA/industry conduct Benefit-Risk (B-R) Assessments
- How premarket B-R Assessment can inform Post Marketing (PM) B-R
- Key Considerations in B-R assessments
- How sponsors and FDA might use B-R Assessments in Decision making
- Communication of PM changes in B-R
- Case Study: Natalizumab

Critical Concepts of Benefit-Risk Assessment

Benefit-Risk across the Lifecycle

- The Benefit-Risk
 Framework is applicable to the post marketing setting
- Advancing systematic B-R
 assessment to support post
 marketing regulatory
 decision making requires
 addressing a number of
 questions

- ✓ When should B-R assessment apply in the post marketing setting?
- ✓ How should post marketing (PM) B-R assessments build on premarket B-R?
- ✓ How do we account for an evolving therapeutic context?
- ✓ How can we best incorporate the highly variable sources of post marketing evidence of a product's benefit and risks?
- ✓ How can we leverage perspectives from patients who have post marketing experience with the product's benefits and harms? 146

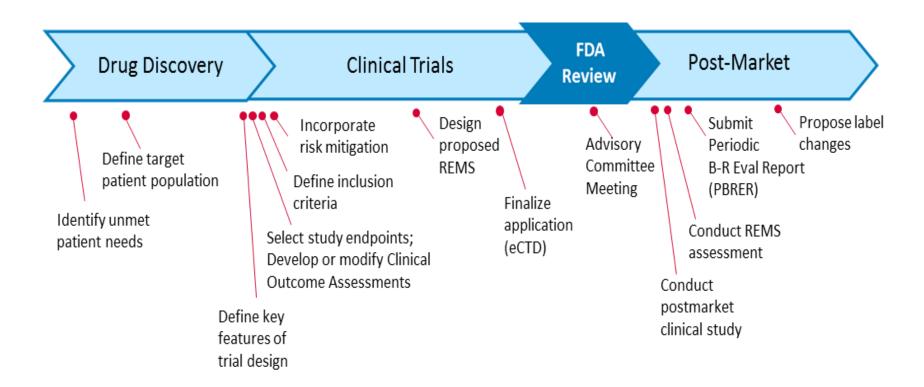


Benefit-Risk: a Continuum

- When: Benefit-Risk assessments occur throughout the lifecycle of a product
- Relevant evidence from pre-market B-R that may inform PM B-R:
 - Risk mitigation may have been evaluated as part of the NDA
 - Relevant BR Considerations: Analysis of Condition, Treatment options, uncertainties, and patient input into disease burden, risk tolerability, unmet need and trade offs
- BR assessment continues informally and formally through PM use as safety information accrues

www.fda.gov

Sample milestones along the medical product lifecycle that may have a particular bearing on benefit-risk assessment of a marketing authorization





Some Sources of Drug Safety Information





FDA Monitors Information for Safety Signals

- Labeling Supplements
- Periodic Benefit Risk Reports (PBRERs) or PSURs-usually contain informal BR assessments
- Literature-case reports, study results, meta analyses
- Spontaneous reports (FAERS)-case review, data mining
- Safety findings from an sNDA, PMR, PMC, sponsor or FDA study (ex. Sentinel)
- Risk Evaluation and Mitigation Strategy (REMS)
 Assessments



What is a Safety Signal

• Information that arises from one or multiple sources (including observations and experiments), which suggests a new potentially causal association or a new aspect of a known association, between an intervention and an event or a set of related events.."*

*CIOMS IX 2014



Post-Market Safety Signal Assessment

Signal Identification:

Potential safety concern identified

Signal Refinement:

Initial evaluation of safety concerns

Signal Evaluation:

Detailed assessment



Examples of Possible Concerns

- -New adverse drug reaction
- -Potential adverse drug reaction
- -Medication error
- -Ineffective REMS
- -Evidence of lack of effectiveness
- -Other (quality issue potentially impacting safety or efficacy)



- For many regulatory decisions, such as a routine update to a product label, the regulatory assessments guiding these decisions do not require a formal evaluation of benefits and risks
- A safety concern may arise that requires a formal B-R assessment to inform regulatory decision making that may lead to
 - -initiation of a REMS
 - Inclusion of a boxed warning
 - Marketing withdrawal

FDA's Benefit-Risk Framework for Human Drug Review

Dimension	imension Evidence and Uncertainties Conclusions a					
Analysis of Condition						
Current Treatment Options						
Benefit						
Risk and Risk Management						
Conclusions Regarding Benefit-Risk						



PM Considerations in a formal B-R

- Seriousness of potential harm
- Therapeutic context
- Medical need met for patients
- Uncertainties surrounding risk
- Potential impact of regulatory action on health care providers' and patients' decision-making
- Potential to manage B-R:
 - with labeling
 - Is additional risk minimization required i.e. REMS



Managing the Risks of Medicines - REMS

- A REMS is a required Risk Management Plan that uses tools beyond the prescribing information to ensure that the benefits of certain drugs outweigh their risks.
- May include:
 - Medication Guide or Patient Package Insert
 - Communication Plan
 - Elements to Assure Safe Use
 - Implementation Plan
- Must include:
 - Timetable for assessment



Possible Measures of Risk Minimization effectiveness

- REMS assessments monitor the effectiveness of the REMS
- A formal study, for example a PMR or FDA study which can include drug utilization use limited to those who achieve the benefit where the risk tolerance is acceptable



Opportunities for Communication of B-R information

- Prescribing Information
- PBRERs (sponsor)
- Dear Doctor Letters (sponsor)
- Drug Safety Communications (FDA)
- Safety Supplements (sponsor)
- FDA Advisory Committee Meetings (FDA and sponsor)
- ?other

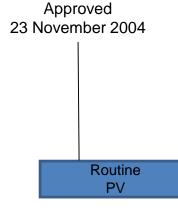


Opportunities for Patient input into B-R

- FDA Public Meetings
- Patient focused Drug Development (FDA)
- Patient and Disease Advocacy Groups
- Patient Registries
- Sponsor Outreach:
 - Input into risk minimization strategies (REMS) pre and post market
 - PROs
 - Surveys
 - New technologies: ex-mobil apps

Case Study: Natalizumab - Approval

- Integrin receptor antagonist
 - Binds to $\alpha 4$ -subunit of $\alpha 4\beta 1$ and $\alpha 4\beta 7$ integrins
- Initially approved to reduce frequency of clinical exacerbations in patients with relapsing form of multiple sclerosis
- Routine monitoring in place



Natalizumab – First Cases of PML

 Within three months of approval, two cases of progressive multifocal leukoencephalopathy (PML) reported in multiple sclerosis patients

Approved 23 November 2004

Marketing suspended 28 February 2005 PML is a rare, serious, progressive neurologic disease, usually occurring in immunosuppressed patients, often resulting in irreversible neurologic deterioration and death.

- Marketing was suspended
- Intensive evaluation of all data

Routine Intensive Evaluation





Therapeutic Context & Benefit

Dimension	Evidence and Uncertainties	Conclusions and Reasons		
Analysis of Condition	 Natalizumab was originally approved in 2004 for relapsing forms of multiple sclerosis (MS), which frequently progresses to severe disability and/or death. 	 Multiple sclerosis is a serious and potentially life-threatening disease. 		
Current Treatment Options	 Natalizumab was a novel treatment mechanism for MS. Other effective treatments were available at the time of approval, but a substantial number patients remained untreated for many reasons, including lack of efficacy or tolerability of existing treatments. 	A significant unmet need existed for more efficacious, better tolerated treatments.		
Benefit	 Previously-approved drugs for MS required clinical trials showing evidence of benefit through two years. The results of Tysabri were so promising that accelerated approval was granted based on one year of data. 	 Natalizumab demonstrated substantial benefit with regards to reduction in relapse rates. 		
	 Additional efficacy evidence submitted in response to the accelerated approval requirement) strengthened FDA's assessment of the drug's benefit. 			
Risk & RM	Next slide			

^{*}Information in this section draws from materials presented by FDA at a 2014 public workshop on Characterizing and Communicating Uncertainty in the Assessment of Benefits and Risks of Pharmaceutical Products, available at: http://nationalacademies.org/hmd/Activities/Research/DrugForum/2014-FEB-13.aspx



2006 Natalizumab B-R Considerations

Risk and Risk Management

Dimension	Evidence and Uncertainty	Conclusions and Reasons
Risk and Risk Mgt	 In the review of natalizumab safety, FDA sought to determine the magnitude of the risk of PML to patients exposed to natalizumab. In total, 3 cases were identified in a population of ~3000 patients. The overall risk of infections (serious and non-serious) was similar for natalizumab vs. placebo. However, the drug appeared to cause an increased rate of specific serious infections, including PML. 	 The submitted additional evidence increased FDA's confidence that the PML cases were caused by natalizumab. The assessment did not resolve uncertainties regarding underlying risk factors, including use of immunosuppressing drugs and duration of natalizumab use. Concerns also included the inability to (a) identify individual patients who are at greater risk of contracting PML, and (b) to mitigate death or other serious effects of PML.



2006 Natalizumab B-R Considerations

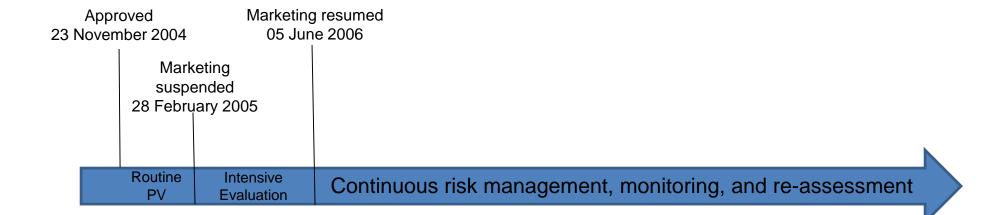
Benefit-Risk Integrated Assessment

- The question FDA faced was whether the risk of PML (and residual uncertainty about that risk) outweighed the substantial benefit of the drug to MS patients.
- 2006 Advisory Committee Meeting: Patients, family, and health care providers testified
 to the difference that Natalizumab had made in the lives of MS patients, as well as the
 willingness of patients to continue treatment despite the risk of PML.
- AC voted unanimously to reintroduce Natalizumab to the market. AC also voted unanimously to impose restrictions and requirements on the use of Natalizumab.
- FDA concluded: "in the face of these potential risks, the benefit of treatment with Natalizumab clearly justifies its re-introduction into the market [with certain requirements] ... and that physicians and patients should be given the opportunity to decide if this treatment is appropriate in any given case."

Natalizumab – Marketing Resumed

- Intensive evaluation revealed no additional cases in multiple sclerosis patients
- FDA sought input form experts and the public, including patients

- Marketing was resumed with strict risk management
 - Restricted distribution
 - Pre-infusion evaluations
 - Registry of all patients



Natalizumab – More Updates

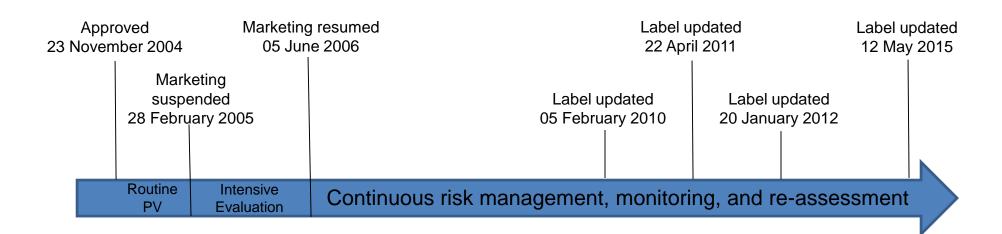
 Label updated in May 2015 to include most recent data on risk factors for PML

Table 1: Estimated United States Incidence of PML Stratified by Risk Factor

Anti-JCV	TYSABRI	Anti-JCV Antibody Positive					Anti-JCV Antibody Positive				
Antibody Negative	Exposure†	No Prior Immunosuppressant Use	Prior Immunosuppressant Use								
	1-24 months	<1/1,000	1/1,000								
<1/1,000	25-48 months	3/1,000	12/1,000								
	49-72 months	6/1,000	13/1,000								

Notes: The risk estimates are based on postmarketing data in the United States from approximately 69,000 TYSABRI exposed patients.

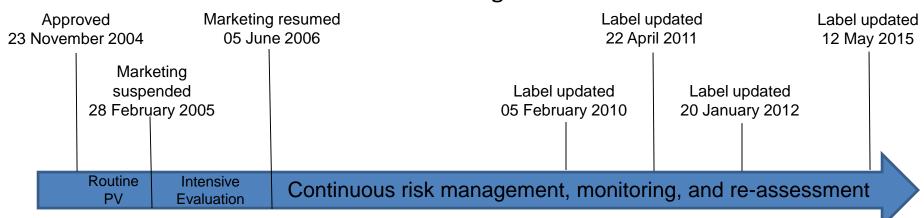
The anti-JCV antibody status was determined using an anti-JCV antibody test (ELISA) that has been analytically and clinically validated and is configured with detection and inhibition steps to confirm the presence of JCV-specific antibodies with an analytical false negative rate of 3%.



[†]Data beyond 6 years of treatment are limited.

Natalizumab – Summary

- Iterative
 - One finding leads to another
- Incremental
 - One step at a time
- Essential
 - Needed for the safe use of the drug





Overall Summary

- New safety concerns may emerge from diverse sources
- As safety concerns are identified, FDA and sponsors may perform B-R assessments related to marketed drugs
- Not all new safety concerns requires a formal B-R assessment for regulatory decision making
- There may be unique considerations in a PM B-R assessments

What are the greatest opportunities for sponsors and FDA to use and communicate the B-R framework in the PM setting?



Acknowledgements

- Robert Ball M.D., M.P.H.
- Gerald Dal Pan M.D., M.H.S
- Sara Eggers PhD
- Graham Thompson

Session 3: Panel Discussion

Using Benefit-Risk Assessment to Inform FDA and Sponsor Decision-Making in the Post-Marketing Setting



Characterizing FDA's Approach to Benefit-Risk Assessment throughout the Medical Product Life Cycle

Using Benefit-Risk Assessment to Inform FDA and Sponsor Decision-Making in the Post-Marketing Setting

Juhaeri Juhaeri Head, Epidemiology and Benefit – Risk Sanofi

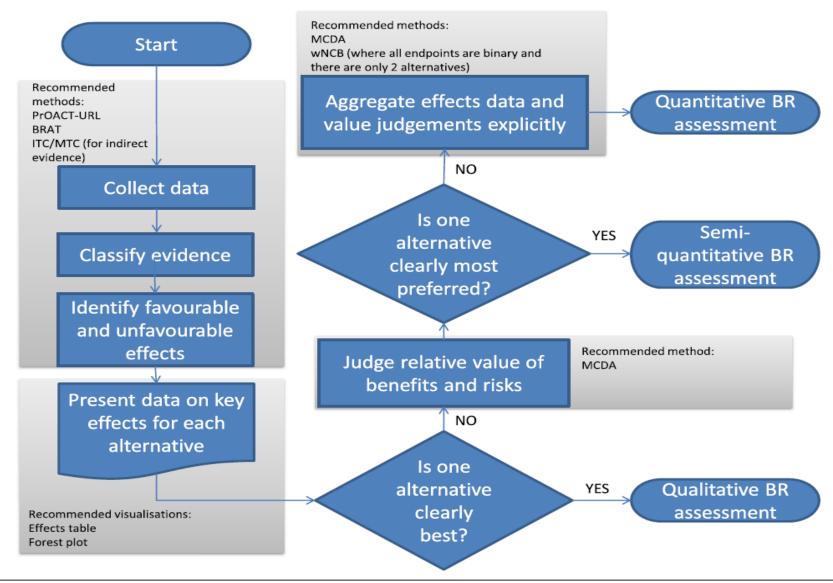


Duke-FDA Benefit-Risk Assessment Silver Spring, MD May 16, 2019 When and how to effectively engage in timely discussions in the post-market setting

- Routine updates: periodic safety reporting
- Signals with serious outcomes: severity, frequency, public health impact
- Clarity on considerations for BR assessment that may be key to post-marketing regulatory decisions
- Quantitative BR, if necessary
- Patient preference, if necessary

When and how to use formal quantitative BR







When and how to use patient preferences



Research & Discovery	Pre-clinical development	Clinic	>	Marketing Authorization	HTA Reimbur		Post- Marketing	
Dis Tar Prototyp	dical need assessment ease familiarization get Product Profile design	_	- Inclusion developm - Treatmen - Acceptate calculation to patien Benefit-risk as - Subpopu	Subpopulation in Benefit-risk weil Early access Labelling optimization esign intification and exclusion criterinent in arm selection on and communication on and communication is seessment rade-off understanding lation identification is sees weighing	ff understanding identification ghing on		Product acceptance Extensions of indicati Post-marketing asses Risk weighing Product innovation mic evaluation Cost-effectiveness analysis Cost-benefit analysis Cost-utility analysis O identification abpopulation identification atcomes weighing ALY estimation	ssments



Patient preferences in benefit-risk assessments



Research & Discovery

Pre-clinical development

Clinical development

Marketing Authorization HTA & Reimbursment

Post-Marketing

Patient-centered benefit-risk assessment (PCBR)

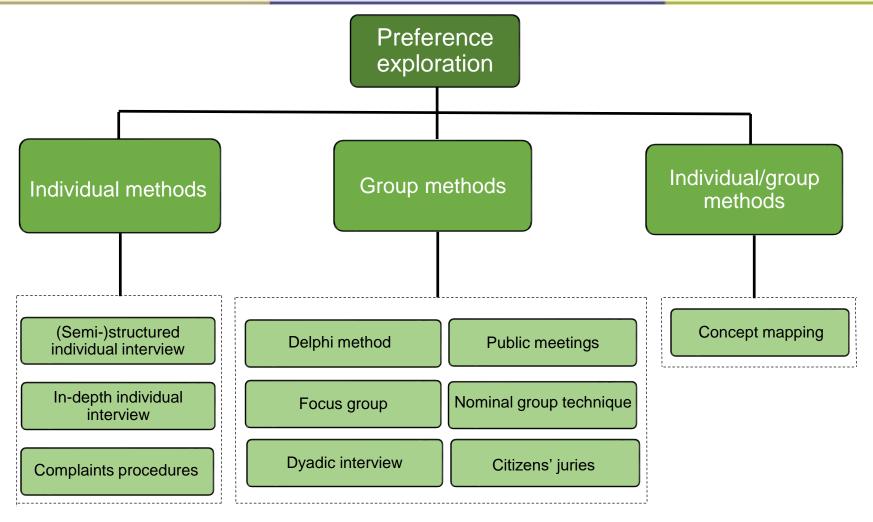
Assessment of:

- Trade-offs between benefits and risks
- Maximum acceptable risk, risk tolerance
- Minimum acceptable benefit, how meaningful the clinical outcome is
- Tolerant sub-populations
 - → Possibility to integrate in MCDA as PPS can elicit weights for clinical outcomes
 - → Need to assess sensitivity of decision to patient preferences



Patient preference methods: qualitative/exploration

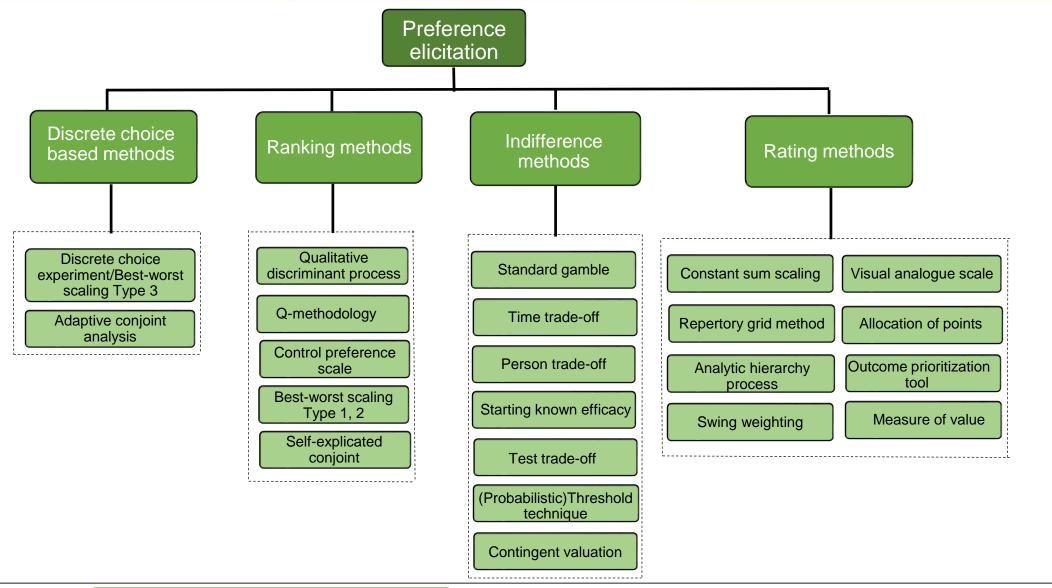






Patient preference methods: quantitative/elicitation







When and how FDA's BR Framework can be used as a communication tool

Labels

- Could contain components of the "grid"
- Condition, treatment options, key benefits and risks, risk management

Safety communications

- Reasons behind safety concern need to be clarified

Public – private partnership:

- To improve clarity on considerations for BR assessment that may be key to postmarketing regulatory decisions
- To develop a guidance on when and how to use formal quantitative BR evaluation
- To develop a guidance on when and how to use patient preference in BR evaluation



Session 3: Panel Discussion

Using Benefit-Risk Assessment to Inform FDA and Sponsor Decision-Making in the Post-Marketing Setting



Session 3: Using Benefit-Risk Assessment to Inform FDA and Sponsor Decision-Making in the Post-Marketing Setting

2:30 pm - 3:45 pm



Session 4: Outlining Next Steps & Future Directions

3:45 pm - 4:30 pm



Discussion of Next Steps and Future Directions

Scott Evans, PhD, MS
Director, The Biostatistics Center
Professor, Department of Epidemiology and Biostatistics
George Washington University

Duke Margolis Center for Health Policy May, 2019



Most clinical trials fail to provide the evidence needed to inform medical decision-making. However, the serious implications of this deficit are largely absent from public discourse.

DeMets and Califf, JAMA, 2011

FDA Advisory Committee Reports

Benefit-Risk Integrated Assessment				
	Benefit-Risk Dimension	าร		
Dimension	Evidence and Uncertainties Conclusions and Reasons			
Analysis of Condition				
Current Treatment Options				
Benefit				
Risk and Risk Management				

The Formula

- Analysis of condition
 - Repeat from the Introduction
- Current treatment options
 - Repeat from the Introduction
- Benefit
 - Repeat the efficacy result
- Risk Management
 - Repeat safety result
 - Theorize how to manage AEs
- Conclusion
 - Benefits outweigh the harms

Benefit:risk evaluation should be pragmatic...

assessing how interventions affect patients.

Segregating benefits and harms is not pragmatic.

Example

- We measure the duration of hospitalization
- Shorter duration is better ... or is it?

- The faster the patient dies, the shorter the duration
- Interpretation of an outcome needs context of other clinical outcomes for the same patient
- Why do we analyze them separately?

Quiz

- Suppose a loved one is diagnosed with a serious disease
- You are selecting treatment
- 3 treatment options: A, B, and C
- 2 outcomes, equally important
 - Treatment success: yes/no
 - Safety event: yes/no

A (N=100)

B (N=100)

C (N=100)

Success: 50%

Success: 50%

Success: 50%

A (N=100)

B (N=100)

C (N=100)

Success: 50%

Success: 50%

Success: 50%

Safety event: 30%

Safety event: 50%

Safety event: 50%

A (N=100)

Success: 50%

Safety event: 30%

B (N=100)

Success: 50%

Safety event: 50%

C (N=100)

Success: 50%

Safety event: 50%

Which treatment would you choose?

A (N=100)

Success: 50%

Safety event: 30%

B (N=100)

Success: 50%

Safety event: 50%

C (N=100)

Success: 50%

Safety event: 50%

Which treatment would you choose?

Choose A...right?

A (N=100)

Success: 50%

Safety event: 30%

B (N=100)

Success: 50%

Safety event: 50%

C (N=100)

Success: 50%

Safety event: 50%

Success

		+	-
SE	+	15	15
	_	35	35

Success

+	-
50	0
0	50

+	-
0	50
50	0

A (N=100)

Success: 50%

Safety event: 30%

B (N=100)

Success: 50%

Safety event: 50%

C (N=100)

Success: 50%

Safety event: 50%

Success

		+	-
SE	+	15	15
	-	35	35

Success

+	-
50	0
0	50

+	-
0	50
50	0

A (N=100)

Success: 50%

Safety event: 30%

B (N=100)

Success: 50%

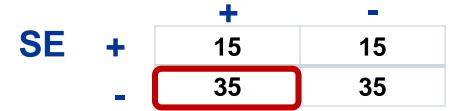
Safety event: 50%

C (N=100)

Success: 50%

Safety event: 50%

Success



Success

+	-
50	0
0	50

+	-
0	50
50	0

A (N=100)

Success: 50%

Safety event: 30%

B (N=100)

Success: 50%

Safety event: 50%

C (N=100)

Success: 50%

Safety event: 50%

Success



Success

+	-
50	0
0	50

+	-	
0	50	
50	0	

What is the Question?

- We define analysis populations
 - Efficacy: ITT population
 - Safety: safety population
- Efficacy population ≠ safety population
- We combine these analyses into benefit:risk analyses. To whom does this analysis apply?
- Personalized medicine? We are not analyzing the patient.

A Vision

STATISTICS IN BIOPHARMACEUTICAL RESEARCH 2016, VOL. 8, NO. 4, 386–393 http://dx.doi.org/10.1080/19466315.2016.1207561



Using Outcomes to Analyze Patients Rather than Patients to Analyze Outcomes: A Step Toward Pragmatism in Benefit:Risk Evaluation

Scott R. Evans^{a,b} and Dean Follmann^c

^aDepartment of Biostatistics, Harvard University, Boston, MA, USA; ^bCenter for Biostatistics in AIDS Research, Harvard University, Boston, MA, USA; ^cNational Institute of Allergy and Infectious Diseases (NIAID) of the National Institutes of Health (NIH), Bethesda, MD, USA.

The good physician treats the disease. The great physician treats the patient.

William Osler

Scott's father (a math teacher) to his confused son many years ago:

"The order of operations is important..."

HEALTHCARE EPIDEMIOLOGY

INVITED ARTICLE

Robert A. Weinstein, Section Editor

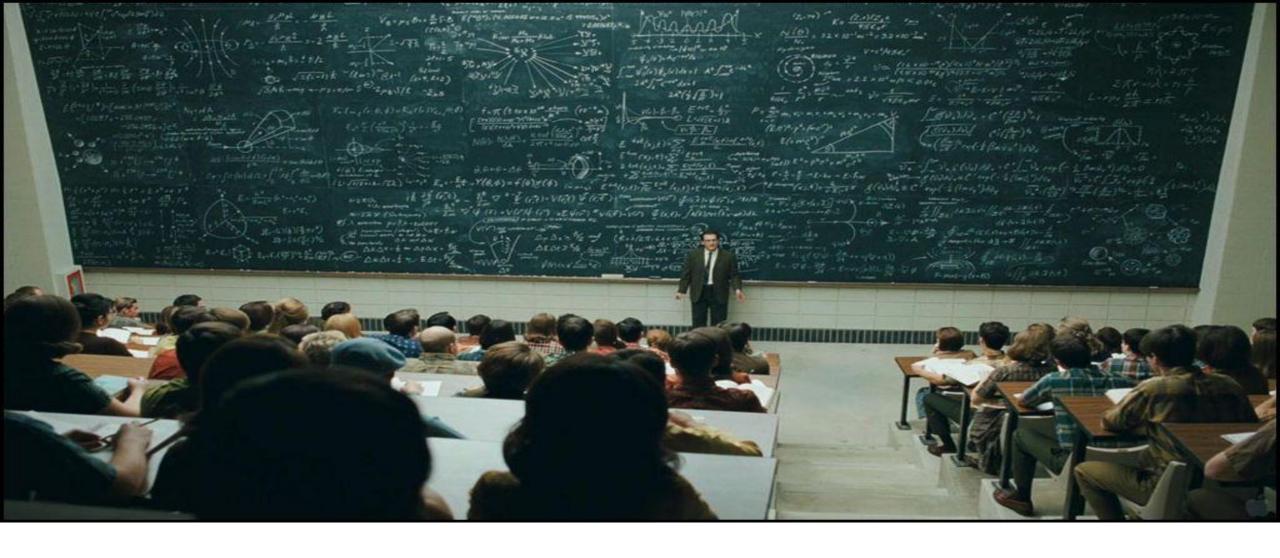
Desirability of Outcome Ranking (DOOR) and Response Adjusted for Duration of Antibiotic Risk (RADAR)

Scott R. Evans,¹ Daniel Rubin,² Dean Follmann,³ Gene Pennello,⁴ W. Charles Huskins,⁵ John H. Powers,^{6,7} David Schoenfeld,⁸ Christy Chuang-Stein,⁹ Sara E. Cosgrove,¹⁰ Vance G. Fowler Jr,¹¹ Ebbing Lautenbach,¹² and Henry F. Chambers¹³

Before we analyze several hundred patients, we must understand how to analyze one.

Summary

- Framework is helpful. It does not go far enough.
- Benefit:risk evaluation should be pragmatic, summarizing effects on patients
- Segregated evaluation of efficacy and safety is not pragmatic
- Encourage framework to include evaluating patients, combining benefits and harms within patient
- Encourage framework to include evaluation of patient preferences in global disease states rather than identifying the value of events



I have no doubt that you will enthusiastically applaud now ...
because you are so relieved that it is over.
Thank you.

Session 4: Outlining Next Steps & Future Directions

3:45 pm - 4:30 pm



Johnson Johnson

Public Meeting: Characterizing FDA's Approach to Benefit-Risk Assessment throughout the Medical Product Life Cycle

Challenges to Advancing Structured Benefit-risk Assessment and Potential Next Steps

Bennett Levitan, MD-PhD
Benefit-Risk Team Lead
Department of Epidemiology
Janssen Research & Development, LLC

OFFICE OF THE CHIEF MEDICAL OFFICER



Disclaimer

The views and opinions expressed in this presentation are those of the author and do not necessarily reflect the official policy or position of Janssen R&D or any of its officers.

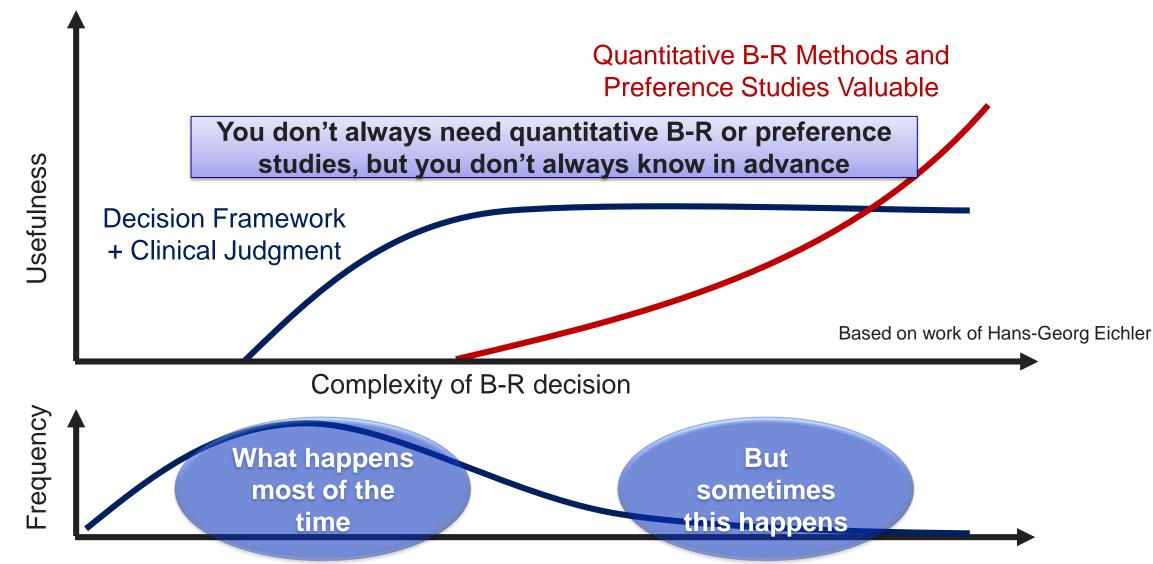


Janssen's Approach to Patient-Focused Benefit-Risk in Development

- Multi-disciplinary team agrees on decision context, value tree (endpoints), approach(es) to B-R assessment and supporting rationale
- B-R statistical analysis plan, technical report
- Patient preference studies if appropriate
- Exploratory analysis and visualization
- Clinical overview, briefing book, Ad Com FDA B-R framework, clear tabular/graphical B-R summaries, preference studies, clinically oriented text/interpretation



When are Quantitative B-R Methods Needed?



Challenges 1: Technical

Value tree

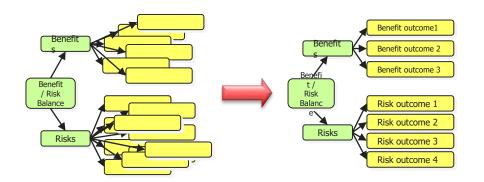
- Multiple perspectives on what are the key endpoints
- Efficacy endpoints + safety endpoints ≠ benefit-risk endpoints
- Often more than one value tree

Effects tables

- Easy for simple studies
- Real world much messier (multiple comparators, treatment paradigms, doses, pooling strategies, ...)

Assumption of independence

- Most B-R analyses tacitly assume independence
- Real world has may have important dependencies



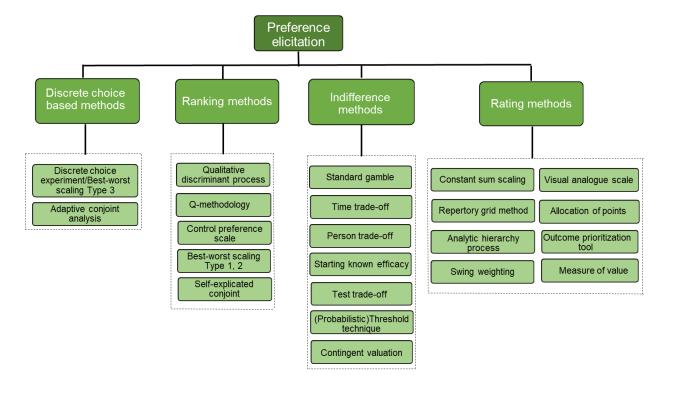
		Rate in Patient-years		
Endpoint	Study [follow up in weeks]	Drug (dose 1)	Drug (dose 2)	Comparat or
Key benefit #1	Study1	XXX	XXX	XXX
	Study2	XXX	XXX	XXX
Key benefit #2	Study1	XXX	XXX	XXX
	Study2	XXX	XXX	XXX
Key benefit #3	Study1	XXX	XXX	XXX
	Study2	XXX	XXX	XXX

	Benefit	No benefit
Harm		##
No harm	##	



Challenges 2: Preference Studies

- General consensus of value for preference studies in B-R, but have open questions for regulatory applications
 - Regulatory standards?
 - Application to clinical data?
 - Impact of shared decision-making?





Challenges 3: Process

- Fitting quantitative approaches into the FDA B-R framework
 - Framework is geared towards qualitative arguments
 - Means to integrate quantitative B-R assessment is not straightforward
- Many techniques and tools in the B-R toolkit
 - Industry and FDA need confidence that they share a common understanding of the potential approaches
 - Want to avoid each company and review division "rediscovering" the same techniques
 - Need for software tools shared between industry and FDA (like SAS code)
- Advance planning of B-R
 - B-R is generally regarded as a post hoc exercise
 - FDA/sponsor analytics is usually prespecified
 - Quantitative B-R is complicated by being partly prespecified and partly post hoc



Potential Next Steps 1

- Public-private partnership (e.g. like MDIC)
 - Neutral ground for sharing of technical, process, legal and pragmatic issues
 - Example topics:
 - Standard to support regulatory applications of quantitative B-R
 - Disseminate best practices avoid each company / review divisions rediscovering the same insights
 - Recommend preference sensitive disease areas (e,g, recent CDRH notice)
 - Mechanism for consortium-based preference studies
- Q&A for ICH M4E(R2) guidance on B-R section
- Collaborate with existing public-private and academic consortia
 - E.g. IMI PREFER, MDIC, ISPOR and IAHPR





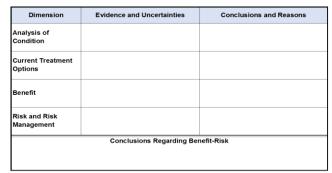






Potential Next Steps 2

- Augment the B-R framework
 - Prompts on qualitative and quantitative patient perspectives
 - Value tree
 - Standard tabular/graphical depictions
 - Place for quantitative B-R
 - Explicit description of value judgments and roles for preference studies
- Guidance
 - 2020 B-R guidance can refer to the potential <u>roles</u> for quantitative B-R
 - Separate FDA guidance to address decision analytic methods and standards
 - Consider update to FDA patient preference guidance that includes considerations from all three divisions and new thinking in the field
 - RWE / post-approval`: When the FDA B-R framework should be updated.
- Capacity building both FDA and industry





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

Document issued on August 24, 2016.
This document will be in effect as of October 23, 20

or questions about this document regarding CDRH-regulated devices, contact the Office e Center Director (CDRH) at 301-796-5900 or Anindita Saha at 301-796-2537

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Food and Drug Administration

Center for Devices and Radiological Health

Center for Biologies Evaluation and Research



Session 4: Outlining Next Steps & Future Directions

3:45 pm - 4:30 pm



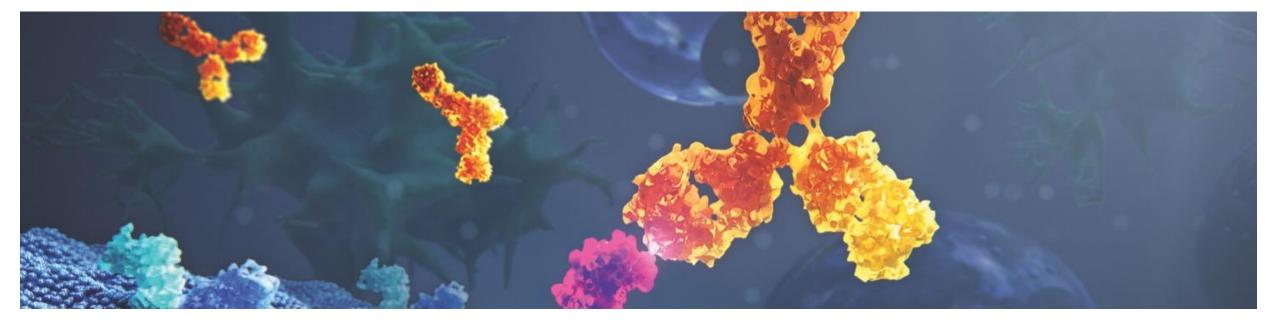


Characterizing FDA's Approach to Benefit-Risk Assessment throughout the Medical Product Life Cycle

Session 4: Outlining Next Steps & Future Directions

Richard Hermann, MD,MPH
Patient Safety Center of Excellence
CMO Organization, AstraZeneca

May 16, 2019



Disclaimer

The views and opinions expressed in the presentation material and commentary are those of the presenter and not necessarily those of AstraZeneca.



What are the key takeaways from this meeting, or considerations for FDA to keep in mind as it develops its guidance on benefit-risk assessment?

- There are many intelligent, motivated people very interested in this topic who are willing to continue to be part of the evolution of thinking and practical application of B-R art and science
- Although B-R assessment is inescapably subjective, as a community we have made big strides forward in this space over the past decade.



What are the most significant challenges to effectively advancing structured benefit-risk assessment for drug development and evaluation over the next five years?

From an organizational level, one continuing challenge is getting all levels of staff across the entire life cycle to embrace the concept that B-R assessment is the most important thing they do on a daily basis.



What next steps can FDA, sponsors, and other stakeholders take to address these challenges?

- Issue practical guidance on organizational approaches:
 - Importance of creating a culture of continuously thinking about the B-R balance
 - Encourage a 'scaffold" of accountability within an organization for some form
 (any form simple or complex) of fit-for-purpose structured approach
 - Keep accurate record of how B-R decisions are made (Who, What, When, Why)
 - Encourage raising Patient Perspective information to the same level as clinical/medical perspective
- Require voting members at advisory committees to take some basic training in the different approaches B-R assessment (???)



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Closing Remarks

Gregory Daniel, Duke-Margolis Center for Health Policy 4:55 pm





Characterizing FDA's Approach to Benefit-Risk Assessment throughout the Medical Product Life Cycle

Tommy Douglas Conference Center • Silver Spring, MD

May 16th, 2019

9:00 am – 4:55 pm

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