U.S. FOOD & DRUG ADMINISTRATION

Benefit-Risk Assessment throughout the Product Life Cycle

Judith Zander, M.D.
Director, Office Pharmacovigilance and Epidemiology
Office of Surveillance and Epidemiology
CDER | US FDA

[Pharmacovigilance and Risk Management Conference
Regulatory Education for Industry] – June 10, 2020

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

Learning Objectives

- Outline the **fundamentals of benefit-risk assessment** in CDER's drug regulatory context

- Describe FDA's **Benefit-Risk Framework** and its implementation in human drug review and post market use

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

"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)

"Safe" is not explicitly defined in statute or regulations

- Interpreted as the determination that a **drug's benefits outweigh its risks**

*For simplicity, the term "drug" is used in this presentation to mean both drugs and biologics
**http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM329758.pdf

FDA's Benefit-Risk Framework

- 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

Benefit-Risk Integrated Assessment

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition		
Current Treatment Options		
Benefit		
Risk & Risk Management		

Therapeutic context for weighing benefits and risks

Product-specific assessments based on available evidence

*Prescription Drug User Fee Act; **Section 905 of the Food and Drug Administration Safety and Innovation Act of 2012

Desired outcomes of the Benefit-Risk Framework

Clear and concise snapshot

- 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

Some key considerations: Therapeutic Context

- **Severity** of the condition and variability across the population
- **Current therapies** and their use in this population
- How well **patients' needs** are met by current therapies
- **Subpopulations** with particular unmet need
- How the current **armamentarium could be enhanced** in terms of safety, efficacy, and tolerability.
- Key **gaps in understanding** patients' needs

Some key considerations: Benefit

- Important strengths and limitations in the **clinical trial evidence**
- **Clinical relevance** of study endpoints
  - How the endpoint relates to how a patient feels, functions, or survives?
  - How important is the clinical effect (e.g., symptom) to patients
- How **clinically meaningful** is the demonstrated benefit to patients
- How the clinical trial evidence will **translate to real-world use**
- **Other benefits** to consider (e.g., more convenient administration)
- Remaining **uncertainties** about the benefits to patients

Some key considerations: Risk and Risk Management

- Extent of the **safety database** (e.g., population exposed)
- Strengths and limitations of **safety assessments**
- Observed **adverse events** and their characteristics
- Potential **safety signals** (e.g., non-toxicological findings)
- Unresolved **product quality** issues
- Potential safety concerns that could **emerge in post-marketing**
- Potential strategies to **mitigate risk** or ensure benefits > risks
- Remaining **uncertainties** about the risks to patients

Culminating in the final analysis

Benefit-Risk Integrated Assessment

- A **concise summary** and integrated analysis
- What **aspects of benefits and risks** factored most into assessment?
- How was **therapeutic context** considered when weighing benefits and risks?
- How will **risk management** help to address key safety concerns?
- Are postmarket activities needed to address **remaining uncertainties**?
- **If Benefits do not outweigh Risks**, what information might lead to a favorable assessment?

Frameworks are available in posted reviews

(drug reviews for FDA approvals are found at drugs@FDA, 2016 and later)

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 $\geq 0.5 \log_{10}$ is associated with reduction in disease progression. The pivotal trial, TMB-301, demonstrated a significantly higher percentage of subjects achieving a $\geq 0.5 \log_{10}$ decrease in HIV viral load after completion of the Essential Monotherapy Period compared with the percentage of subjects achieving a $\geq 0.5 \log_{10}$ 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.

(e.g., TROGAZO [ibalizumab], table portion only), available:
https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/761065Orig1s000SumR.pdf

Approval documentation may include more than one BRF

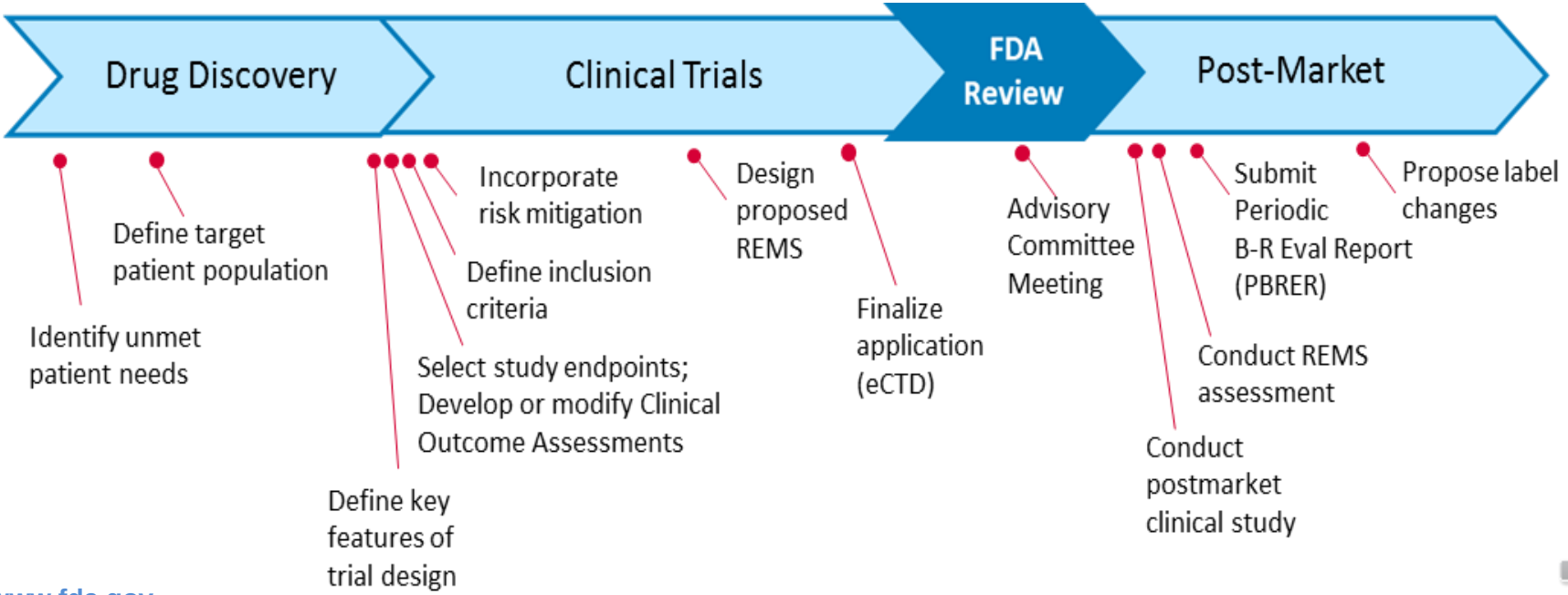
- Some teams complete a BRF at every level of clinical review
- Others have a single BRF completed collaboratively

*for more info, see 2018 Implementation Plan

Benefit-Risk: a Continuum

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

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



Use of Benefit-Risk (B-R) Framework Post Marketing

- 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 PM B-R assessments

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 (e.g., Sentinel)
- Risk Evaluation and Mitigation Strategy (REMS) Assessments

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)

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

PM Considerations in a formal B-R

- 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

Case Study: Natalizumab - Approval

- Integrin receptor antagonist
  - Binds to α4-subunit of α4β1 and α4β7 integrins
- Initially approved to reduce frequency of clinical exacerbations in patients with relapsing form of multiple sclerosis (MS)
- Routine monitoring in place

Approved Nov. 2004

Routine PV

Natalizumab – First Cases of PML

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

- 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

2006 Natalizumab B-R Considerations*

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.	• MS 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. Study results were so promising that accelerated approval was granted based on one year of data. • Additional efficacy evidence submitted in response to the accelerated approval requirement strengthened FDA's assessment of the drug's benefit.	• Natalizumab demonstrated substantial benefit with regards to reduction in relapse rates.
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: 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 Management	• 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 MS 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

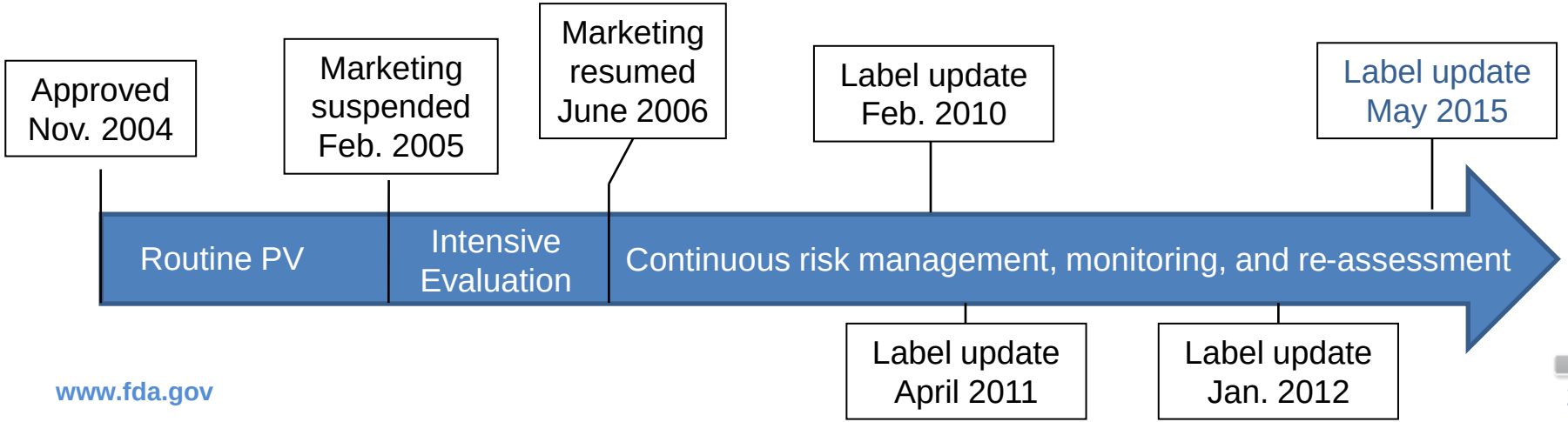
Natalizumab – More Updates

- Labeling continually updated
- In May 2015 the update included most recent data on risk factors for PML

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

Anti-JCV Antibody Negative	TYSABRI Exposure†	Anti-JCV Antibody Positive	
		No Prior Immunosuppressant Use	Prior Immunosuppressant Use
<1/1,000	1-24 months	<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.
†Data beyond 6 years of treatment are limited.
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%.



Resources on Benefit-Risk Assessment

"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

*2012 Fifth Authorization of the Prescription Drug User Fee Act; *2017 Sixth Authorization of the Prescription Drug User Fee Act

Challenge Question #1

Which of the following is NOT a key factor in FDA's Benefit-Risk Framework:

A. Analysis of the condition

B. Risk management

C. Cost evaluation

D. Current treatment options

Challenge Question #2

True or False:

Formal Benefit-Risk assessments are reserved for pre-market review decisions.

False

Summary

- Benefit-Risk assessments occur throughout a product's lifecycle
- 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 PM B-R assessment

Acknowledgements

- Sara Eggers and Decision Support and Analysis Team, CDER, FDA
- Gerald Dal Pan M.D. and Robert Ball M.D., Office of Surveillance and Epidemiology, CDER, FDA

U.S. FOOD & DRUG ADMINISTRATION

Questions?

Judith Zander, M.D.
Director, Office Pharmacovigilance and Epidemiology Office of Surveillance and Epidemiology
CDER | US FDA

[Pharmacovigilance and Risk Management Conference Regulatory Education for Industry] – June 10, 2020