The Challenge of Uncertainty in Regulatory Decision-Making

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Public Workshop: Characterizing and Communicating Uncertainty in the Assessment of Benefits and Risks
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Benefit-Risk Assessment in Human Drug Review

- FDA’s regulatory decisions are based on our assessment of the benefits and risks of the product under review.
- Our laws and regulations provide the boundaries for our decisions.
- Our decisions are informed by an extensive body of evidence, analyzed through the lens of science, medicine, policy, values, and judgment.
- Our benefit-risk assessment places our evaluation of benefits and risks in the context of the underlying disease and available treatment options.

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| Benefit-Risk Summary and Assessment |
What’s On The Regulator’s Mind?

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

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Uncertainty in Drug Regulation

• Even with all the evidence available, uncertainties are present, and they can be significant. For example:
  – Uncertainty in Benefit stemming from
    ▪ Limits in our scientific understanding of a disease
    ▪ Inconsistent or contradictory evidence across multiple studies
    ▪ Relationship between study population and those who will actually take the drug
  – Uncertainty in Risk, stemming from
    ▪ Numerical imbalances of adverse events in treatment and control groups
    ▪ Post-market data from sources of varying levels of rigor
    ▪ Ability of the health care system to adequately manage a risky drug
Decision-Making under Uncertainty

• Drawing conclusions in the face of uncertainty is a complex and challenging task; nonetheless, we must work through it and decide!
• Where uncertainty is high, clinical judgment, values, and input from others (patients, ACs) may have greater role
• We do not yet employ a systematic approach to dealing with uncertainty when it might be helpful
Our Objective for this Workshop

• Identify a potential path forward in developing an approach to working through uncertainty that:
  – Is practical and implementable in the regulatory setting
  – Respects the legal and regulatory framework in which a regulator operates

• Handling uncertainty is not unique to drug regulation, and we included experts in other fields to better understand how they address this issue

• Day 2—Communicating uncertainty