US Perspective on the Regulatory Assessment of Benefit-Risk of Vaccines

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OUTLINE OF PRESENTATION

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INTRODUCTION

• US FDA must ensure the availability of safe and effective vaccines.
• Marketing authorization requires a vaccine to be safe and effective for its intended use.
  – Safety is relative, and thus not explicitly defined in the FDA statutes or regulations
  – All medical interventions whether preventative or therapeutic carry some degree of risk
  – The safety of a vaccine is assessed by determining whether its benefits outweigh its potential risks.
• The FDA’s regulatory decisions in the pre-market and post-market review process are based on the assessment of benefits and risks of the product under review.
INTRODUCTION (CONT’D)

• The FDA considers not only the safety and effectiveness data submitted by the sponsor of a license application, but also considers other factors that may affect their assessment of benefit-risk.
  
  – nature and severity of the disease the vaccine is intended to treat or prevent
  – benefits and risks of other available interventions for the disease
  – availability of risk management tools

• This assessment is informed by the available scientific evidence and clinical judgment in accordance with applicable legal and regulatory standards.

• Although the FDA’s assessment encompasses both a quantitative and qualitative evaluation of scientific and clinical evidence, determining the acceptable degree of risk presents a challenge to regulators and medical policy makers.
BENEFITS VERSUS RISKS

• National Regulatory Authority (USFDA)
  – Evaluates benefits and risks for the population

• HEALTHCARE PROVIDER
  – Evaluates benefits/risks for the patient

• PATIENT
  – Evaluates benefits/risks in terms of personal value
ACCEPTABILITY OF VACCINE RISKS

• Define disease risks
• Define vaccine risks
• Effective communications of vaccine and disease risks
• Defining societal and individual rights
• Parents’ rights in deciding for their children
• Uncertainty and trust: parents and vaccine manufacturers/public health officials
ACCEPTANCE OF RISK

Decisions about health risks are made not only on a scientific basis, but also on a psychological, religious, philosophical, and intuitive basis.

Voluntary, natural and controllable risks are more readily accepted than risks that are imposed, not within an individual’s control, or due to human causes. Risks that are familiar are more readily accepted than those that are unfamiliar or hypothetical.
RISKS: INDIVIDUAL VS SOCIETY

The acceptance of risks that are associated with vaccines depends on:

– the weight that individuals give to societal good versus individual rights.

Is it appropriate to compare the value of lives lost or damaged to vaccine adverse events to those lost or damaged to disease?

– decisions are different when disease incidence is low versus high.

– one must consider that disease incidence is kept low because of the vaccine.

– who accepts the risk of vaccination?
Vaccine Regulatory Decision-Making

- Regulatory decisions that USFDA makes in both the pre-market and post-market drug review process are based on the Agency’s assessment of the benefits and risks of the product under review.

- This assessment is informed by science, medicine, policy, and judgment, in accordance with applicable legal and regulatory standards.

- The intersection of these components constitutes the framework in which FDA makes regulatory decisions.

- This framework begins with FDA’s legal authority embodied in the Federal Food, Drug, and Cosmetic Act (the FD&C Act), the Public Health Service Act (PHS Act) and the regulations that the Agency issues to implement these Acts.
SAFETY

US FDA 21CFR600.3

• The relative freedom from harmful effect to persons affected, directly or indirectly, by a product when prudently administered.

• FDA approval of a product means that FDA has determined that the available data supports the safety and effective of the vaccine for its labeled indication under its labeled conditions of use.
SAFETY

• USFDA’s determination of safety does not suggest an absence of risk.

• A product is considered safe if the clinical significance and probability of beneficial effectiveness outweigh the medical importance of its harmful or undesirable effect.
Vaccine Development

Research and Development
- Discovery
- Development of Manufacturing Process
- Nonclinical Studies
- Preclinical testing

Clinical Development
- IND
- Phase 1
- Phase 2
- Phase 3

BLA Review
- Data Review
- Approval

Postmarketing Surveillance
- Phase 4
- Adverse Event Monitoring
- Inspection
- Lot Release Testing
Vaccine Development & Characterization

- **Purity (21 CFR 610.13)**
  - pyrogenicity
  - moisture content

- **Identity (21 CFR 610.14)**
  - on final container, e.g. SDS-PAGE, Western blot,

- **Other release tests**
  - in process testing critical for safety and manufacturing consistency

- **Sterility (21 CFR 610.12)**

- **General Safety (21 CFR 610.11)**
  - test on final container product
  - detection of extraneous toxic contaminants
Vaccine Production and Quality Control: Common Principles

• Detailed manufacturing procedures: consistency of production
• Defined compatible components
• Product characterization: specifications
• Adventitious agent testing
• Examination for extraneous materials
• Stability, including genetic stability
Preclinical Safety Studies

- Design based on intended clinical use
- Evaluation of product specific concerns
- Testing in animal model for immunogenicity and safety (e.g., toxicity, neurovirulence)
- Reproductive toxicity studies (prior to study specifically enrolling pregnant women)
Vaccine Clinical Trials and Licensing

• As vaccines are developed, they undergo several stages of clinical testing.
  – The vast majority of vaccine candidates are rejected during this process.

• **Results from clinical testing constitute the factual base for risk assessment.**

• Adverse reactions must be distinguished between those that may be caused directly by the vaccine and unrelated events that may occur by coincidence.
USFDA’s Approach to Developing a Benefit-Risk Framework

• A benefit-risk assessment framework must operate within the applicable legal, regulatory, and policy framework for each regulatory decision.

• A systematic approach to benefit-risk assessment should support the regulatory authority’s evaluation throughout the lifecycle of a drug by capturing the full range of decisions from pre-market review through any regulatory actions that are necessary in the post-market setting.

• It should facilitate identification of the critical issues regarding benefit and risk and capture the regulatory authority’s deliberation on those issues.

• The approach should also focus discussion and communication on the weighing of those issues, ensuring that benefit and risk are considered throughout review.

• Finally, a systematic approach should efficiently integrate into a review teams’ existing processes and work products.
Benefit-Risk Considerations that Influence Regulatory Decisions and Recommendations

• Identification of demonstrated benefits and risks through regulatory review of submitted evidence

• Risk management considerations, e.g., recommended labeling language

• Information about the disease to be treated or prevented versus benefits-risks of other available interventions

• Benefit-risk Summary Assessment
Qualitative versus Quantitative Approaches to Benefit/Risk Assessment

• The term “quantitative benefit-risk assessment” can have various meanings depending on who is asked.
• Quantitative benefit-risk assessment may encompass approaches that seek to quantify benefits and risks, as well as the weight that is placed on each of the components such that the entire benefit-risk assessment is quantitative.
  – This approach is typical of quantitative decision modeling.
  – It usually requires assigning numerical weights to benefit and risk considerations in a process involving numerous judgments that are at best debatable and at worst arbitrary.
• Application of quantitative decision modeling seems most appropriate for decisions that are largely binary.
• Many benefit-risk assessments are more nuanced and conditional based on parameters that could be used to effectively manage a safety concern in the post-market setting.
Qualitative

• There is concern that reliance on a complex quantitative model may obscure rather than elucidate a regulator’s deliberation.

• These concerns have led USFDA to the conclusion that the best presentation of benefit-risk considerations involves focusing on the individual benefits and risks, their frequency, and weighing them appropriately.
  – this can be accomplished by a qualitative descriptive approach for structuring the benefit-risk assessment
  – quantification of certain components of the benefit-risk assessment is an important part of the process to support decision-making
  – USFDA considers it important to be clear about what was considered in the decision, to be as quantitative as possible in characterizing that information, and to fully describe how that information was weighed in arriving at a conclusion

• Quantitative assessments may underpin the qualitative judgments of USFDA’s regulatory decisions, but USFDA has adopted a structured qualitative approach that is designed to support the identification and communication of the key considerations in FDA’s benefit-risk assessment and how that information led to the regulatory decision.
US FDA Structured Approach to Benefit Risk Assessment in Drug Regulatory Decision Making

- Coincides with industry and other NRAs (e.g.; EMA)
- Defines context in which regulatory decision is made
- Identifies relevant information/data regarding benefit risk
- Assesses information with respect to its bearing on the decision
- Draws conclusions from information based on expert judgment
- Communicates the decision and rationale
SUMMARY

• NRAs are the first public line in evaluating benefit versus risk of vaccines
  – Benefit-risk assessment is built into the regulatory review
• Regulatory decisions both pre- and post-marketing are based on assessment of benefits and risks
• The expertise of the NRA is utilized to make decisions based on the benefits and risks for populations
• Labeling and previous experience with the system’s ability to manage benefit-risk are factors in considering a product for approval
• Risks are minimized throughout the product lifecycle
• Modeling and research efforts for are ongoing
• US FDA has developed a Structured Approach to Benefit Risk