Considerations for New Product Planning in Light of FDA Draft Guidance on Benefit-Risk Assessment

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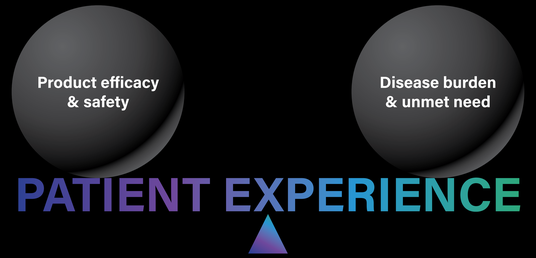
BACKGROUND

The US Food and Drug Administration (FDA) conducts a benefit-risk assessment during the regulatory review of marketing applications for new products. This assessment provides a structured and transparent view of the evidence, uncertainties, and reasoning that support regulatory decision-making. Currently, the focus is on the product's pharmacology, efficacy, and safety.

The fifth authorization of the Prescription Drug User Fee Act (PDUFA V) included commitments for the FDA to increase the clarity, transparency, and consistency of the FDA's benefit-risk assessments in drug evaluations. The 21st Century Cures Act also requires the FDA to incorporate relevant patient experience data and related information into regulatory decision-making.

Accordingly, in 2021, the FDA released draft guidance for industry on benefit:risk assessment for new drug and biological products. This guidance is intended to clarify how the FDA considers a drug's benefits, risks, and risk management options when making regulatory decisions. This emerging guidance suggests an evolution towards more holistic approaches to drug evaluation, incorporating evidence on disease burden and unmet need, particularly from patient/caregiver perspectives, alongside product efficacy and safety.



OBJECTIVE

The anticipated FDA benefit:risk assessment guidance provides manufacturers with opportunities to update approaches to disease-state and clinical research supporting product development, starting at the preclinical stage. Our recommendations for new product planning incorporate the four **dimensions discussed in the draft guidance:**

Stages of product development:

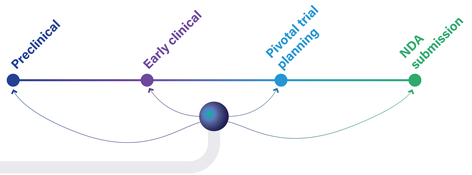


Table 1: Recommendations for new product planning

Dimension (per FDA draft guidance)	Preclinical	Early clinical	Pivotal trial planning	NDA submission
Analysis of condition	**Collect literature-based evidence and identify key gaps** • How serious is the condition? • What is the typical duration and time course? • How does the condition impact patients, ie, symptoms and functional status?	**Develop evidence plan to address gaps** • Demonstrate what aspects of the condition have the greatest impact on patients, eg, incidence, duration, clinical complications, quality of life, key subpopulations • Articulate any public health implications of the disease	**Ensure that trial design addresses key concerns with the condition** Utilize patient preference information to inform clinical development planning	**Connect concerns with the condition to attributes of the product** Identify what aspects of the condition (eg, symptoms, complications) are targeted by the product
Current treatment options	**Conduct treatment landscape review and identify the unmet need** • Are there subgroups who have suboptimal efficacy or excessive safety concerns with available options? • Is there an important treatment outcome for which existing therapies have not demonstrated efficacy? • Is there evidence that reflects the patient perspective on current treatment and unmet need?	**How serious is the condition? Develop evidence plan to more clearly define unmet need** • Articulate the unmet need based on efficacy, safety, tolerability, treatment burden, etc. • Specifically develop evidence demonstrating the patient perspective, if currently available evidence is limited	**Ensure that trial design provides product the opportunity to demonstrate that it addresses unmet need** Include planned analyses to identify outcomes in subgroups likely to experience the most benefit and/or the lowest risk	**Connect the product to impact on unmet need** • Define how the product addresses efficacy and/or safety gaps among current treatment options • Include how the product addresses unmet need as described by patients themselves
Benefit	**Define benefit in this indication:** • What are the strengths and limitations of different trial designs? • What benefits are most meaningful to patients? • What are the clinically relevant endpoints that measure outcomes that are important to patients?	**Use early trials to seek evidence of benefit and to inform pivotal trial design**	**Select design and endpoints that align with accepted measures of benefit** Include endpoints that capture the patient experience: how the patient feels, functions, or survives	**Clearly articulate the benefit based on pivotal trial results:** • Impact of the product on key outcomes, eg, survival, symptoms • Importance, magnitude, duration/time course, and uncertainty of the results • Outcomes in key subgroups • Patient-meaningful product features such as treatment burden
Risk and risk management	**Define what would be considered risks in the indication:** What adverse effects are most concerning for patients overall or in specific subgroups?	**Use early trials to identify safety signals and other risks and to inform pivotal trial design**	**Design the trial to minimize risk and maximize safety** Include approaches to clearly identify and quantitate risk and to determine how risk differs among patient subgroups and over time	**Clearly articulate the risks with an emphasis on management** • Provide context on the risk, such as how pivotal trial results are expected to compare with real-world outcomes • Define how to predict, prevent, monitor for, and manage adverse events **Develop labeling that appropriately conveys the benefits and risks, to allow patients and providers to conduct informed individual benefit-risk assessments** The draft FDA guidance notes that benefits and risks must be considered for the overall indicated population but should also consider individual patient perspectives

RESULTS

Table 1 presents recommendations for new product planning that takes the FDA draft guidance into consideration. These recommendations include:

Conducting disease state research (eg, literature-based research, patient/caregiver experience, real-world evidence)	**Clearly defining benefit and risk in the indication**	**Designing clinical trials to measure more broadly defined risk and benefit**

In general, activities to support FDA evaluation under the new guidance are also relevant to US payers and value assessors (eg, Institute for Clinical and Economic Review [ICER]) and would inform global health technology assessment (HTA) submissions, but with key differences:

The FDA guidance considers disease burden and unmet need through the lens of risk imposed on patients, caregivers, and society When considering disease burden and unmet need, payers and value assessors focus on direct and indirect costs alongside the clinical picture of the disease	**The FDA guidance weighs the drug's clinical outcomes as risks and benefits** Payers and value assessors ultimately translate clinical outcomes into economic outcomes such as cost effectiveness

CONCLUSION

The draft FDA guidance on benefit:risk assessment provides an opportunity to optimize evidence planning starting at the preclinical stage and continuing throughout product development, in a manner largely consistent with preparation for regulatory evaluation and HTA in key global markets. Our approach outlines how early evidence planning can incorporate both benefit:risk and economic considerations to optimize regulatory and payer submissions. These recommendations will be revisited upon finalization of the FDA guidance.

ACRONYMS

FDA: Food and Drug Administration
HTA: Health technology assessment
ICER: Institute for Clinical and Economic Review
NDA: New drug application
PDUFA: Prescription Drug User Fee Act

REFERENCES

US FDA. Enhancing Benefit-Risk Assessment in Regulatory Decision-Making. September 2021. Available at: https://www.fda.gov/industry/prescription-drug-user-fee-amendments/enhancing-benefit-risk-assessment-regulatory-decision-making. Accessed April 17, 2022.

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