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Food, Drug & Device Law Alert - FDA Issues Draft Guidance On Factors To Consider When Making Benefit-Risk Determinations For IDEs

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The Food and Drug Administration (FDA) recently issued a draft guidance titled, "Factors to Consider When Making Benefit-Risk Determinations for Medical Device Investigational Device Exemptions (IDEs)." According to the FDA, "[t]he purpose of this guidance is to provide greater clarity for FDA staff and investigational device exemption (IDE) sponsors and sponsor-investigators regarding the principal factors that FDA considers when assessing the benefits and risks of IDE applications for human clinical studies."

The early sections of the draft guidance summarize familiar principles of IDEs, including informed consent, the regulatory standard for IDE decisions, the types of IDE decisions, study design considerations, stages of device development and the associated varying uncertainty and risk tolerance, and the general benefit-risk determination in the IDE context.

The final section of the draft guidance includes a fairly lengthy discussion of the many specific considerations that go into making benefit-risk determinations for IDEs. Overall, "FDA recommends using a benefit-risk framework to facilitate the incorporation of evidence and knowledge from different domains—clinical, nonclinical, and patient—to support a comprehensive, balanced decision-making approach." The specific factors addressed in the draft guidance are summarized below:

Patient preference – consistent with another recent draft guidance (summarized here) on obtaining valid scientific evidence of patient preferences, FDA reiterates that "[w]hen available, information characterizing subject tolerance for risk and perspective on benefit may provide useful context for assessing the benefits and risk of a proposed clinical investigation."

Investigational device description – a complete and accurate understanding of the investigational device is important to the IDE decision.

Risk assessment – in general, the draft guidance recommends IDE sponsors use an accepted method of risk assessment, such as ANSI/AAMI/ISO 14971 on which the draft guidance relies. The type of risks identified are:

- Risk to study subjects, including:
    - Type of risk and severity, including basic safety, device-related adverse events (serious and non-serious), procedural-related complications, risk associated with the

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study itself, risk from false-positive or false-negative results for diagnostics

    - Likelihood or probability of risk
    - Duration of risk and potential harm
    - Risk management, including device design features/modifications, protective measures (e.g., study design features), and communication of safety information
- Other risk considerations:
    - Risks related to study data (false conclusions or inconclusive data) and benefit of knowledge to be gained
    - Risks to others, e.g., participating healthcare practitioners

Assessment of Direct Benefit to Study Subjects – Factors include:

- Type of benefits, including device's anticipated impact on clinical management, subject health, and subject satisfaction in the target population, such as improving clinical management and quality of life, reducing the probability of death, aiding improvement of subject function, reducing the probability of loss of function, and providing relief from symptoms
- Magnitude of benefits
- Probability of the patient experiencing one or more benefits
- Duration of effect(s)

Assessment of benefits to others – includes the benefit of the knowledge to be gained

Other factors to consider:

- Characterization of the disease - i.e., the treated or diagnosed condition, its clinical manifestation and severity (e.g., temporary or permanent loss of function), how it affects the subjects, how and whether a diagnosed condition is treated, and the condition's natural history and progression
- Availability of alternatives - treatment (or diagnostic) options, treatment strategy (if applicable, such as for chronic diseases) and the safety and effectiveness of alternatives including the potential for adverse events
- Subject tolerance for risk and perspective on benefit
- Uncertainty, including the factors below:
    - Quality of prior nonclinical and clinical investigations
    - Predictive ability of evidence from prior investigations
    - Different uncertainty considerations at different stages of

development

- Least burdensome study design: FDA does not consider cost when deciding to approve an IDE application, but the potential impact of study design elements on trial start-up, IRB approvability, and feasibility of subject enrollment should be considered

The draft guidance elaborates somewhat on many of these factors and concludes with two appendices, the first setting forth a proposed outline for sponsors to follow when summarizing the primary benefits and risks of a proposed IDE and the second setting forth hypothetical examples.

A copy of the draft guidance document can be found here.

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