FDA Guidance: Benefit-Risk

AMDM FOCUS Meeting

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Los Gatos

Guidance Background and Scope

- For Reviewers during Pre-Market Review- predictability, consistency, transparency
- Applicable to PMA's and *de novo* petitions
- Diagnostic and Therapeutic Devices
- Consider for design, non-clinical testing, pre-IDE, IDE, assembling application/petition
- Relies upon valid implementation of ISO 14971 during design and development.

Risk-Benefit Determination

- Scientific Evidence
  - Clincial
  - Non-Clinical
- Probable Risk
- Probable Benefit
- Not-theoretical

Factors Considered

(within intended use)

- Types of Benefits for Diagnostics
  - Identify a specific disease
  - Prevent spread of disease
  - Predict future disease
  - Earlier diagnosis
  - Probably treatment

Factors Considered

(within intended use)

- Magnitude of Benefits
- Probability of one or more benefits
- Duration of Benefit

Factors Considered

(within intended use)

- Assessment of Risk for Diagnostics
  - False Positive or False Negative
  - In aggregate
- Uncertainty
  - Severity of disease
  - Availability of Alternatives (unmet medical need?)
  - Risk mitigitation through complementary test

Hypothetical Example

- Serum Based IVD differentiates BI-RADS 4 mammography results into two groups:
  - Recommend waiting
  - Proceeding to Biopsy

Hypothetical Example

- Intended Use:

  The in vitro diagnostic test measures 10 peptide analytes and yields a single qualitative result. The test is intended for females 40 years or older following mammography of a breast lesion with a BI-RADS of 4 result to aid physicians in the decision to recommend a breast biopsy.

  Negative test result (Low Risk): immediate biopsy is not recommended, wait a few months for further tests.

  Positive test result (High Risk): immediate biopsy is recommended.

Hypothetical Example

IVD Result	Biopsy Result		Total
	Malignancy	Benign	
Positive	97	75	172
Negative	3	225	228
	100	300	400

Sensitivity=97% (97/100) with 95% two-sided
CI: 91.5% to 99.0%
Specificity=75% (225/300) with 95% two-sided
CI: 69.8% to 79.6%
Prevalence=25% (100/400)
NPV=98.7% (225/228)
PPV=56.4% (97/172)

Hypothetical Example

- Benefits:

  Avoiding morbidity associated with an immediate biopsy for the 57% (228/400) of subjects whose test results indicate a low probability of having breast cancer.

- Risks:

  Among test-negative subjects, the observed (from immediate biopsy) prevalence of cancer is 1.3% (3/228 = 1-NPV). The main risk from use of the device is in failing to biopsy some BI-RADS 4 patients who have biopsy-detectible breast cancer, thus delaying their diagnosis and treatment. Concerning this risk, the sponsor asserts that a clinically acceptable prevalence for cancer among non-biopsied BI-RADS 4 subjects is 2% or lower.

Hypothetical Example

- Additional Factors:
  - There are the usual uncertainties tied to statistical confidence intervals surrounding observed study results.
  - No weighting for clinical impact, that is, the type of benefit is not necessarily commensurate with the type of risk.
  - There is uncertainty about the extent of the probable risk(s)/harm(s) (sponsors assertions of 2%).
  - Test-negative BI-RADS 4 patients, who do not undergo biopsy, will receive no histopathological assessment of benign disease that is present.

Hypothetical Example

- Additional Factors:
  - Patient tolerance for delayed diagnosis and treatment of breast cancer typically is low. This needs to be weighed against the value that patients place on avoiding biopsy-related morbidity.
  - There are no other in vitro diagnostic devices cleared or approved for the new test's intended use.
  - All women with negative test results will have follow-up visits for further evaluation and testing.

Hypothetical Example

Approval/Non-Approval Considerations:

- probabilities of benefits and risks reasonably defined.
- clinical practice reference for acceptable risk presented and test's perf. characteristics aligned.
- Weighting of the different kinds of benefits versus risks is not directly addressed
- additional information is needed to establish whether the trade-offs are acceptable.

Not approvable, but FDA would likely take it to an advisory panel prior to making a decision.

Hypothetical Example

Conclusion

Given that the benefits are uncertain and the risk (for a very small number of patients) could be substantial, FDA might determine that this device is not approvable, but would likely take it to an advisory panel prior to making a decision.

Hypothetical Example

What kind of Questions might FDA ask of the Advisory Panel?

Example based on Actual FDA Benefit-Risk Determinations

- permanently implanted cardiovascular monitoring device intended to diagnose heart failure.
- study shows that its use reduces the number of hospitalized days for subject due to heart failure.
- implantation procedure for the device requires -1 day patient hospitalization.
- similar devices on the market provide similar level of benefit and do not require an implantation procedure.
- FDA determined not approvable.

Factor	Questions to Consider	Notes
Assessment of Benefits of Devices		
Type of benefit(s)	- What primary endpoints or surrogate endpoints were evaluated? - What key secondary endpoints or surrogate endpoints were evaluated? - What value do patients place on the benefit?	Avoidance of morbidity from breast biopsy procedures.
Magnitude of the benefit(s)	- For each primary and secondary endpoint or surrogate endpoints evaluated: o What was the magnitude of each treatment effect? - What scale is used to measure the benefit? o How did the benefit rank on that scale?	Avoiding inconvenience, pain and potential complications associated with breast biopsy procedure.
Probability of the patient experiencing one or more benefit(s)	- Was the study able to predict which patients will experience a benefit? - What is the probability that a patient for whom the device is intended will experience a benefit? - How did the benefits evaluated vary across sub-populations? (If the study was sufficiently powered for subpopulations, note specific subpopulations, nature of difference and any known reasons for these differences.) - Was there a variation in public health benefit for different populations? - Even if the benefit is in a small portion of the population, do those patients who would experience the benefit value it?	Approximately 57% (228/400), for the intended use population.
Duration of effect(s)	- Could the duration, if relevant, of each treatment effect, including primary and secondary endpoints be determined? If so, what was it? - Is the duration of the benefit achieved of value to patients?	Variable. Might be long term (no biopsy needed, lifelong), or might last only until follow-up exam prompts a biopsy.

Factor	Questions to Consider	Notes
Assessment of Risks of Devices		
Severity, types, number and rates of harmful events (events and consequences):		
· Δεϖιχε–ρελατεδ σεριουσ αδϖερσε εϖεντσ	- What are the device-related serious adverse events for this product?	Some patients with biopsy-detectible breast cancer will not have the cancer detected/treated until follow-up exam (assuming that follow-up exam occurs).
· Δεϖιχε–ρελατεδ νον–σεριουσ αδϖερσε εϖεντσ	- What are the device-related non-serious adverse events for this product?	Failure to characterize non-malignant disease that would have been revealed by biopsy.
· Προχεδυρε–ρελατεδ χομπλιχατιονσ	- What other procedure-related complications may a patient be subject to?	N/A
Probability of a harmful event	- What percent of the intended patient population would expect to experience a harmful event? - What is the incidence of each harmful event in the study population? - How much uncertainty is in that estimate? - How does the incidence of harmful events vary by subpopulation (if applicable)? - Are patients willing to accept the probable risk of the harmful event, given the probable benefits of the device?	For the most serious harmful events, approximately 1% (3/400) in the intended use population. Slightly more than 1% (3/228) among test-negative subjects.
Duration of harmful events	- How long does the harmful event last? - Is the harmful event reversible? - What type of intervention is required to address the harmful event?	Potentially lifelong, if treatable/curable breast cancer is not detected.
Risk from false-positive or false-negative results for diagnostics	- What are the consequences of a false positive? - What are the consequences of a false negative? - Is this the only means of diagnosing the problem, or is it part of an overall diagnostic plan?	See above.

Factor	Questions to Consider	Notes
Additional Factors		
Uncertainty:		
· Θυαλιτψ οφ τηε στυδψ δεσιγν	- How robust were the data?	There is no assurance that the clinical impact of breast cancers missed among patients with BI-RADS 4 mammography results is equivalent to the clinical impact of breast cancers among patients who have BI-RADS 3 results. Hence, there is uncertainty about the extent of the probable risk(s)/harm(s).
· Θυαλιτψ οφ τηε χονδυχτ οφ τηε στυδψ	- How was the trial designed, conducted and analyzed? - Are there missing data?	Good.
· Ροβυστνεσσ οφ τηε αναλψσισ οφ τηε στυδψ ρεσυλτσ	- Are the study results repeatable? - Is this study a first of a kind? - Are there other studies that achieved similar results?	Reasonably robust.
· Γενεραλιζαβιλιτψ οφ ρεσυλτσ	- Can the results of the study be applied to the population generally, or are they more intended for discrete, specific groups?	The relative value that patients place on avoiding biopsy morbidity, compared to the clinical impact of missing a biopsy-detectible cancer, is not known.
Characterization of the Disease	- How does the disease affect the patients that have it? - Is the condition treatable? - How does the condition progress?	The disease is very severe.
Patient tolerance for risk and perspective on benefit	- Did the sponsor present data regarding how patients tolerate the risks posed by the device? - Are the risks identifiable and definable?	Patients' tolerance for delayed diagnosis and treatment of breast cancer typically is low. This needs to be weighed against the value that patients place on avoiding biopsy-related morbidity.
· Δισεασε σεϖεριτψ	- Is the disease so severe that patients will tolerate a higher amount of risk for a smaller benefit?	Disease is very severe and affects patients' quality of life.
· Δισεασε χηρονιχιτψ	- Is the disease chronic? - How long do patients with the disease live? - If chronic, is the illness easily managed with less-invasive or difficult therapies?	The disease is chronic, potentially incurable and, in some cases, fatal.

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