U.S. FOOD & DRUG ADMINISTRATION

OSMA Fall 2024 Meeting
De Novo Decision Analysis: Answers To Your Questions

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“De Novo Decision Analysis”?

- The “De Novo decision analysis” refers to an assessment of MDUFA IV De Novos by OPEQ/ORP staff to understand what’s happening with De Novos:
  - De Novo granting rate: ~40-50%
  - 510(k) substantial equivalence (SE) rate: ~85%
  - PMA original/panel-track approval rate: ~80%
- The assessment included:
  - Data we can pull from our tracking systems
  - A manual assessment of a representative cohort of 59 De Novos (~20%) over MDUFA IV
    - A range of questions capturing the administrative record
    - Balanced for fiscal year, granted/not granted, and OHT
- We presented this to the MDUFA industry group in May 2024.

MDUFA IV Cohort Overall

- 64% of M4 De Novo cohort had small business designation
  - 510(k)s: 46%
  - PMAs: 16%
- Differences in outcomes between “small” and “large” businesses
- 81% of M4 De Novos had a Pre-Submission; primary difference is between granting and withdrawals
- 80% of accepted M4 De Novos were placed on hold
  - 60% of De Novos that responded to an AI letter were granted

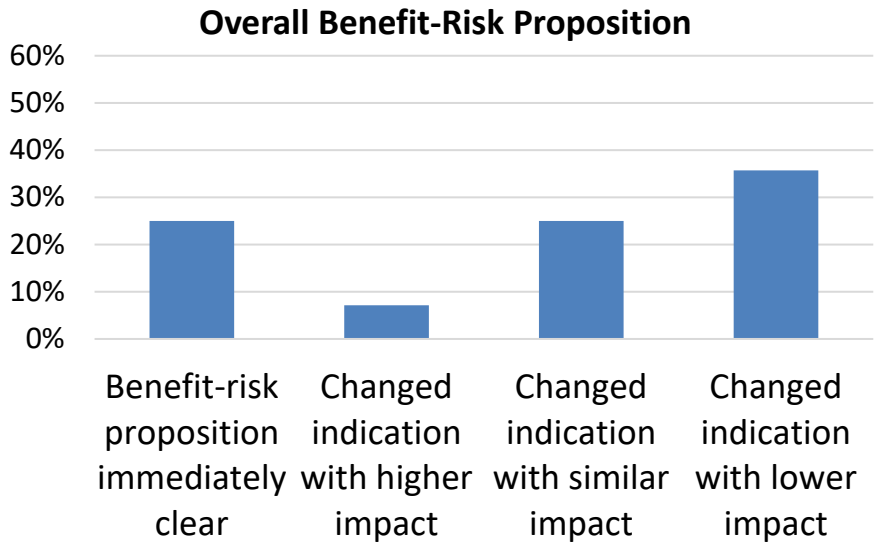
Small Business	Small	“Large”	Total
Granted	42.2%	54.5%	46.6%
Declined	27.1%	14.5%	22.6%
Ineligible	5.2%	0.9%	3.6%
Withdrawn	15.1%	24.5%	18.7%
Deleted	10.4%	5.5%	8.5%

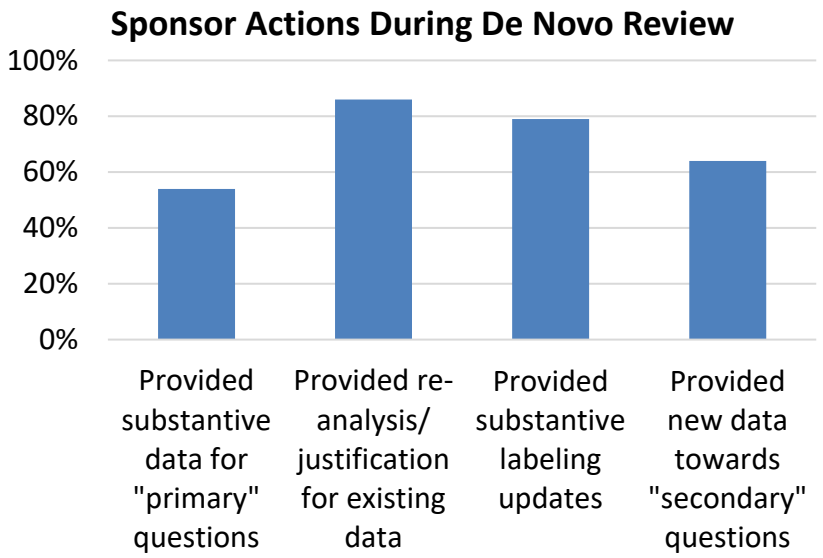
Pre-Submission	Yes	No	Total
Granted	50.2%	30.4%	46.6%
Declined	22.1%	25.0%	22.6%
Ineligible	3.6%	3.6%	3.6%
Withdrawn	15.7%	32.1%	18.7%
Deleted	8.4%	8.9%	8.5%

Accepted submissions only

[Federal Register :: Medical Device User Fee Rates for Fiscal Year 2024]

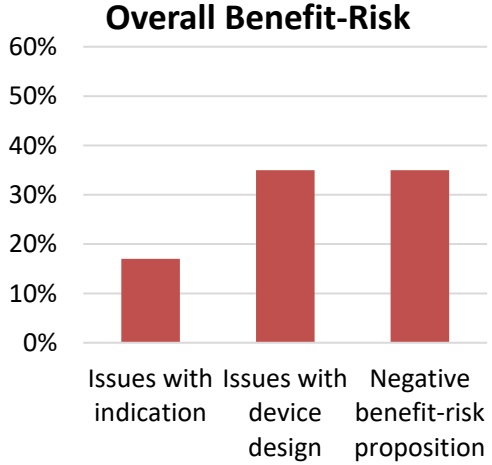
Granted Decision Analysis

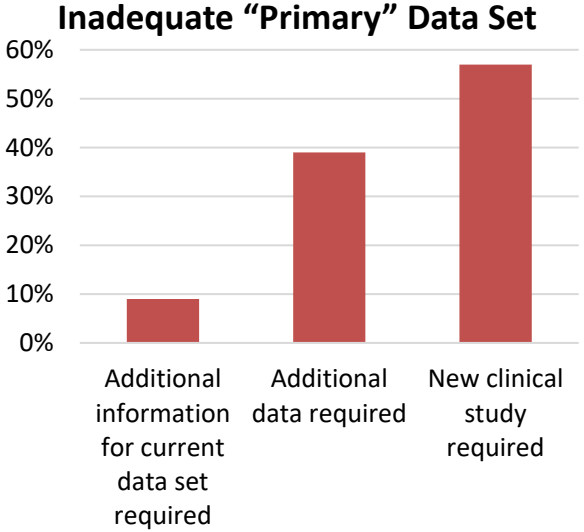


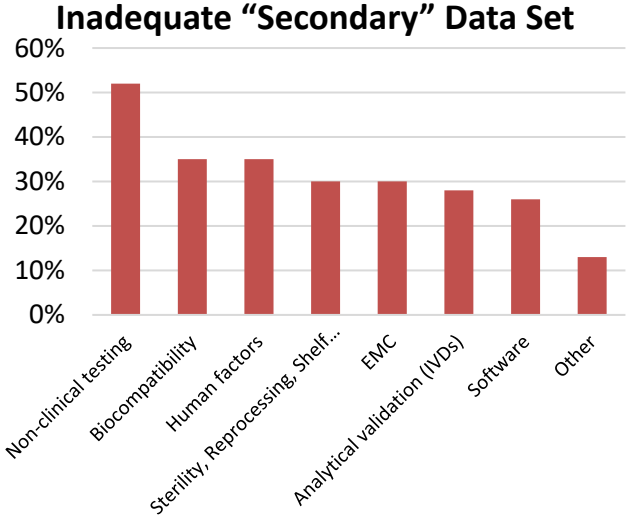


- Most De Novos do not have a “slam-dunk” benefit-risk proposition upon first review.
- Most De Novos use the course of review to provide additional data and address FDA concerns.
- Note: “primary” refers to fundamental benefit-risk proposition of the device; “secondary” refers to cross-cutting issues important for risk mitigation (e.g. biocompatibility, EMC)

Not Granted Decision Analysis







- The reasons identified for De Novos that were not granted were varied. In the majority of cases where there were concerns with the primary data set, FDA requested a new clinical study altogether.
- Note that this data includes administrative records that did not always get to a formal decline decision (e.g., files that did not respond after receiving an AI letter).
- Note also that "primary" refers to fundamental benefit-risk proposition of the device; "secondary" refers to cross-cutting issues important for risk mitigation (e.g. biocompatibility, EMC)

Differences in Benefit-Risk

- These tables represent individual review teams' yes/no assessments of benefits and risks, not ORP staff.
- Not all items should apply in all situations (e.g., single-arm studies).
- Not granted De Novos did not always reach a formal decline decision.
- **FDA did not always find clear and overwhelming evidence of benefit, even for granted De Novos.**

Top differences in benefit between granted and not granted De Novos

Stated benefit	Granted	Not granted
Benefit that is meaningful considering condition	52%	7%
Met minimum clinically important difference	37%	13%
Equivalent performance with other modalities	30%	7%
Benefit equal to or greater than control	48%	33%
No evidence of benefit	0%	33%

Top differences in uncertainty in benefit between granted and not granted

Stated uncertainty in benefit	Granted	Not granted
Confounding interventions/physiological factors	22%	0%
Large amounts of missing data	22%	33%
Inconsistent or conflicting results	4%	40%

Note: Not a complete list of all factors; only the largest numbers and differences (> 10% between granted/not granted) are reported.

Differences in Benefit-Risk

- Generally, there were fewer differences in risk between granted and not granted De Novos.
- Granted De Novos would appear to be slightly higher risk devices overall, though this is not a clean conclusion.

Top differences in risk between granted and not granted De Novos		
Stated risk	**Granted**	**Not granted**
Adverse events from device use/procedure	37%	20%
False positives/false negatives	30%	27%

Top differences in uncertainty in risk between granted and not granted De Novos		
Stated uncertainty in risk	**Granted**	**Not granted**
Poor or inconsistent adverse event definitions	19%	7%
Lack of data on repeated exposure to device	11%	0%
Confounders – comorbidities, other treatments	11%	0%
Inconsistent or conflicting results b/w studies	4%	20%

Note: Not a complete list of all factors; only the largest numbers and differences (> 10% between granted/not granted) are reported.

Other Data

- Pre-Submissions
  - **70%** (**75%**/**65%**) of De Novos had a Pre-Submission.
  - **19%** (**29%**/**10%**) of De Novos had an IDE. (Of all De Novos with IDEs, **73%** were granted.)
  - **34%** (**38%**/**30%**) of De Novos had the indications for use meaningfully change over the Pre-Submission history.
- Eligibility
  - **36%** of the time, the sponsor believed they were a 510(k), but were told otherwise prior to the De Novo submission.
  - De Novo eligibility was raised in Pre-Subs (**48%**), 513(g)s (**3%**), or a 510(k) submission (**28%**).
- Completeness
  - **37%** (**32%**/**42%**) of De Novos had studies that were not yet completed at the time of submission.
  - **47%** (**61%**/**35%**) of <u>original</u> De Novos had sufficiently addressed prior feedback.
- 2nd De Novo request
  - **12%** of De Novos were previously declined. Of those De Novos, **28%** were granted.

Combined (**Granted**/**Not granted**)

YOUR QUESTIONS

Clinical Data as a Special Control

- The principles for establishing clinical data requirements as a special control are the same as for any special control:
  - Must be the least burdensome means of mitigating risk, i.e., no other means (e.g., bench testing or animal testing) of mitigating a particular risk
  - Required for all devices within the new regulation
  - Must consider how clinical data will be used in substantial equivalence determination

Clinical Data as a Special Control

- Depends in part on benefit-risk proposition of the regulation and whether it has been adequately defined by the De Novo device.
- Why might it be necessary to require clinical data?
  - No way to understand how device will behave in real-world clinical use
  - Can't extrapolate benefit from bench testing or animal testing
  - Mechanism of action is not well understood (example: "magic box" device)
- Why might clinical data be unnecessary moving forward?
  - "Proof of concept" has been demonstrated for the class of device
  - Non-clinical data is a sufficient surrogate for how a device behaves in vivo
- Remember that FDA is the final arbiter of what special controls are needed to provide reasonable assurance of safety and effectiveness.

Increased Use of Postmarket Special Controls

- Postmarket special controls are an evolving area and FDA has used them recently in several De Novos to reach granting decisions. Postmarket special controls implementation includes:
  - Pre/postmarket balance as FDA deems necessary, including terminating postmarket requirements
  - Explicit postmarket study outlines directly in the granting order (similar to other postmarket requirements language)
- The increase in recent approvals with postmarket special controls is not tied to any specific action or decision by FDA.
- Postmarket special controls are a double-edged sword.
  - No gating as with 522 postmarket study requirements
  - Not complying with special controls places you out of the regulation
  - Labeling updates following postmarket studies can impact the overall perception of your device

The Benefit-Risk Proposition

- The benefit-risk worksheet is not a calculator in which reviewers tally wins and losses. It is there to ensure that FDA has assessed all benefit-risk factors in its decision-making and acknowledged what has been demonstrated in an objective manner.
- Recognize that there may be inherent differences between how FDA views your benefit-risk proposition and how you view it. You might agree with FDA if you were standing in our shoes.
- Speak in the language of uncertainty and speak truthfully as to why FDA should be willing to accept the uncertainty associated with your device.
- Recognize that FDA has to make a decision based on the data we have now, not the data the company expects to collect in the future.

Brainstorming Opportunities

- Better use of the Q-Sub process, such as:
  - FDA "**state of the De Novo**" templates that are provided to sponsors at the end of each feedback
  - **30-Day Pre-Sub for clinical trial design review** for non-IDE studies
  - Sponsor **Pre-De Novo Q-Subs**, to provide a preview of the entire submission before the De Novo is received, and provide an opportunity for critical discussions
- Limitations of the De Novo statute/regulations
  - We do not have **filing** requirements for De Novos
  - We do not have "**not approvable**" decisions for De Novos (as with PMAs) and our **AINN response times** are shorter relative to PMA
- Reassessing approach for "**low benefit, low risk**" De Novos with additional regulatory tools

Inspections for De Novos

- FDA reserves the authority to inspect De Novo facilities (1) for data integrity purposes and (2) to understand critical or novel manufacturing processes (21 CFR 860.240(c)).

Legal Interpretations and De Novo

- Given the complexities of the De Novo classification process, how do you foresee legal interpretations impacting the future of medical device regulatory approvals and the balance between innovation and safety?
  - The De Novo process is established by the FD&C Act and by regulation. It serves as an important pathway to establish appropriate controls for low to moderate risk devices, which streamlines the market introduction of innovative devices.
  - Each De Novo by definition is a unique type of device, but we work very hard to achieve consistency in how we review De Novos and in how we grant them.

Key Challenges in Collecting Clinical Evidence for De Novos

- With the increasing use of the De Novo pathway for novel medical devices, what are the key challenges the FDA faces in ensuring robust clinical evidence for these devices?...
  - Structural issues faced by companies, like regulatory expertise, business timelines, medical device company milestones, and capital
  - Companies collecting data with significant margin to support robust FDA authorization vs being carried to the finish line
  - Getting companies and FDA on the same page and having critical conversations about opportunities and limitations
- …and how is the agency addressing these challenges to maintain high standards of safety and effectiveness?
  - Total Product Lifecycle Advisory Program (TAP)
  - FDA strives to communicate/collaborate to set up companies for success.
  - But keep in mind: "Should this have marketing authorization?" and "Is it ***actually*** a good product?" are two different things.

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