De Novo Process

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De Novo Updates

- **Draft Guidance: "*De Novo* Classification Process (Evaluation of Automatic Class III Designation)"** - *Issued October 3, 2011*
- **FDASIA changes to *de novo*** - *July 2012*

Novel Device – *De Novo* or PMA?

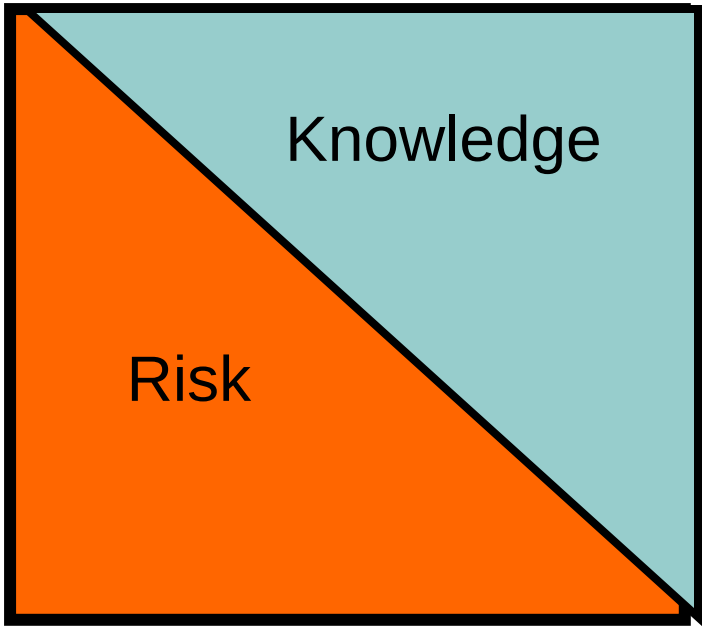
- Is a *de novo* submission appropriate for my device?

How are IVD Devices Classified?

Questions?

- Regulatory path determined using a risk-based approach
- Classification (I, II, or III) depends on risk

Class I – most 510(k) exempt



Low likelihood of harm

Class II - 510(k)

High or unknown likelihood of harm,

or how to prevent harm is unknown

Class III - PMA

Advantages of *De Novo* Submission

- PMA application may be more complex than a *de novo* submission
- PMA review and approval may take more time than a *de novo* review
- No PMA supplements and usually no post market reports for a *de novo* approved device
- Cost
  - PMA is $248,000 ($62,000 for a small business or free if the first submission) (2013 Fee Schedule)
  - *De novo* through a 510(k) is $4,960 ($2,480 for a small business). Free if *de novo* done as a direct *de novo* (2013 Fee Schedule)

Risk is Dependent Upon Intended Use

- Risk (and subsequently classification and submission type) is inherently tied to the Intended Use of a device.

Risk is Dependent Upon Intended Use

- Level of FDA review and type of studies requested generally depend on the Intended Use claims; not always on type of technology or assay

- Prostate-specific antigen (PSA) testing with an indication for
  - "aid in detection of prostate cancer" (PMA)
  - "monitoring prostate cancer patients for disease progress" (510(k))

Use Established IVD Devices as a Starting Point

- Search our Classification Database to view classification and required submission type information for devices similar to yours:

- http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpcd/classification.cfm

Use Established IVD Devices as a Reference

- Search our PMA and 510(k) Databases to compare your device claims to established intended use claims:

- http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/pma.cfm?IVDProducts=on

- http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm?IVDProducts=on

Is My Device First-of-a-Kind?

- Can the device be placed under existing regulations?
- Devices with novel technologies can often fit into the existing regulatory framework

Ask FDA For Device Regulation Information

- 513(g) – Official request for information about how FDA believes a device would be classified

- Pre-submission – Informal interactive process allowing early assessment of device class, and least burdensome regulatory route to getting the device on the market

Understanding De Novo

Before the FDA Modernization Act:

- **Section 513 (f)(1) of the Food, Drug and Cosmetic Act (the FD & C Act) automatically classified devices that were not in commercial distribution prior to May 28, 1976 into Class III, requiring a pre-market approval (PMA)**

Understanding *De Novo*

FDA Modernization Act of 1997:

- **Provided a new mechanism for classifying new devices for which there is no predicate device**
- **Allowed an automatic class III designation to be evaluated and overturned**
- **Appropriateness was determined on a case by case basis and was risk based**

FDA Modernization Act of 1997 (FDAMA) - New Section 513(f)(2) of the FD & C Act. Amended November 21,1997

De Novo Candidates

- Lower risk IVDs for which there is no predicate
- Ancillary to other well-accepted methods for diagnosing a condition
- Discuss with FDA first before you begin the process

Not a Candidate

- High risk IVDs,
- Devices with risks that could not be managed to provide a reasonable assurance of safety and effectiveness, or
- Devices for which a predicate device exists.
- *De novo* process cannot be used to reclassify a device if there exists a legally marketed device upon which to base a determination of substantial equivalence.

To Find Other *De Novo* Devices

- Search Federal Register (FR)

- Search 510(k) Database (through OIVD website)
  http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm?IVDProducts=on
  - Under “type” select: “De Novo Petitions Granted”
  - Under “panel” select Chemistry, Immunology, etc.

- Search Transparency Page on *De Novos*
  http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDRH/CDRHTransparency/ucm232269.htm

Draft *De Novo* Guidance

- **One of 25 Action Items from FDA's "Plan of Action for Implementation of 510(k) and Science Recommendations"**
  - Provide updated recommendations for interacting with FDA
  - Clarify the FDA review process
  - Describe the recommended content
- Original *de novo* guidance released in 1998

Guidance Goals

- Earlier, more productive, discussions between FDA and Industry
- More comprehensive *de novo* submissions
- More transparent and predictable *de novo* review practices

The De Novo Process

- A classification process
- Review process for safety and effectiveness

De Novo Process Comparison

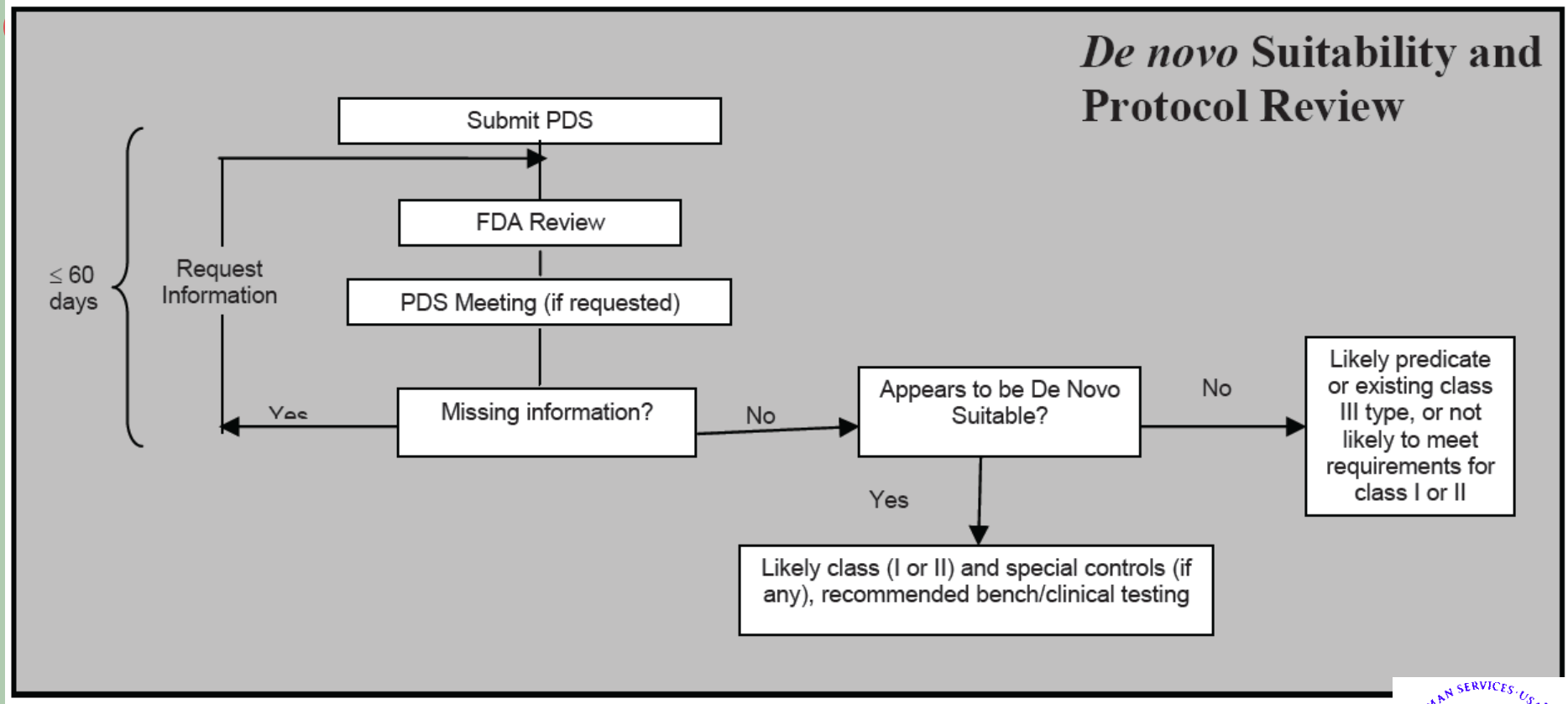
Current Process:

FDA and sponsor discuss possibility of *de novo* application informally through a teleconference or Pre-submission.

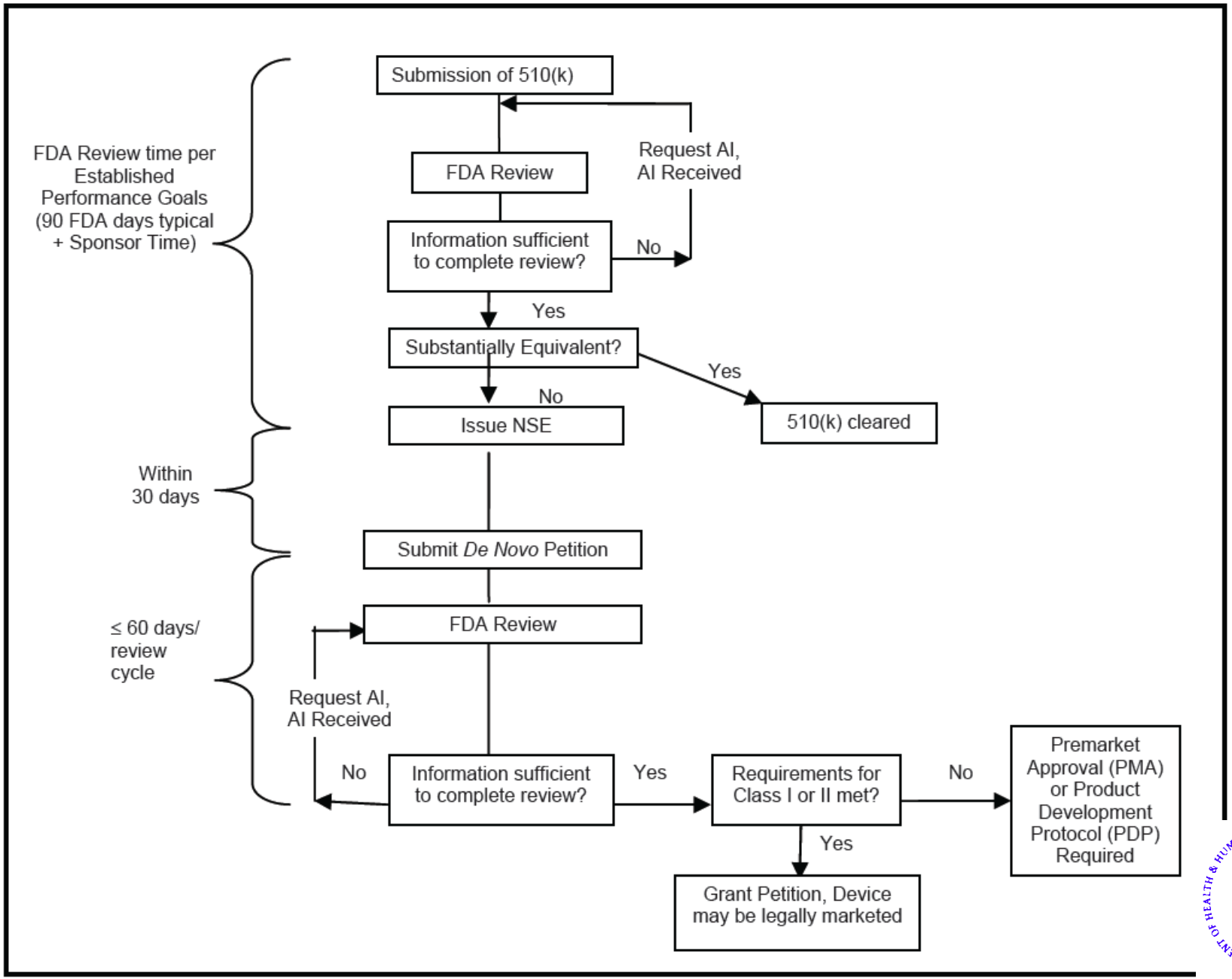
Proposed Process in Draft Guidance:

FDA and sponsor discuss possibility of *de novo* application more formally through a Pre *De Novo* Submission (PDS)

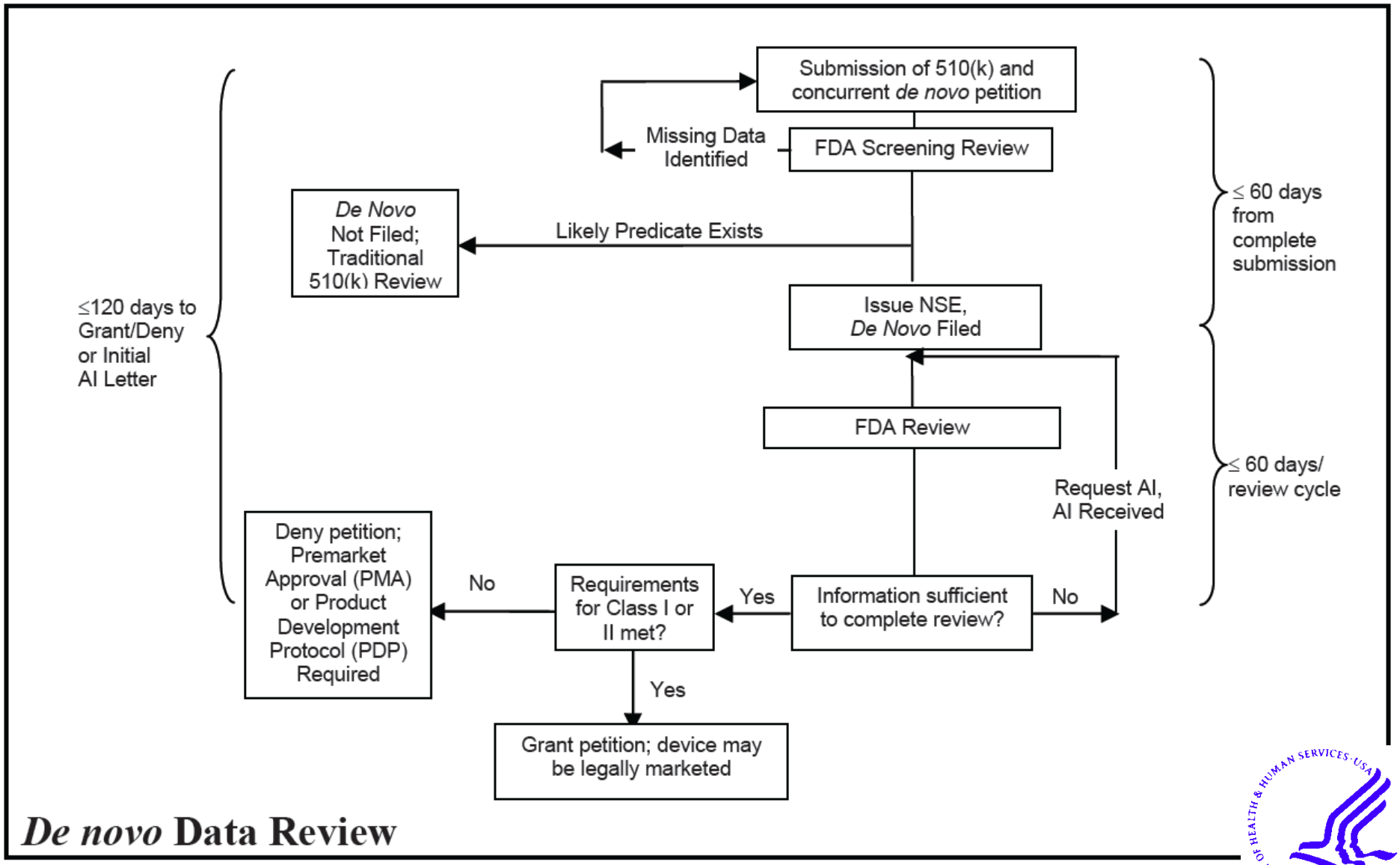
Proposed PDS Process



Proposed De Novo Review – Traditional



Proposed De Novo Review – After PDS



***De novo* Data Review**

Main FDASIA Changes

- FDASIA left traditional *de novo* pathway (510(k) and then a *de novo* submission) (Fee associated)
- FDASIA added a direct *de novo* pathway (*de novo* submission only) (No fee associated)
- FDASIA allows the FDA a 120 day review period after submission of a *de novo* submission

After Completion of *De Novo* Studies

Current Practice Post FDASIA:

- De novo applications are submitted to the FDA as (1) a 510(k) followed by a *de novo* submission (*de novo* 510(k)s) (Fee associated) or (2) a direct *de novo* submission (No fee associated)
- FDASIA allows the FDA a 120 day review period after submission of the *de novo* submission for both paths

Proposed in Guidance:

- Concurrent submission of 510(k) and *de novo* petition
- Review of data **not** likely complete at time of NSE (60 FDA days)

De Novo Language from NSE Letter:

- The Act provides for the Evaluation of Automatic Class III Designation (de novo) in section 513(f)(2). Under this section any person whose device is found to be not substantially equivalent to a device type that has not been previously classified, can request FDA to make a risk-based classification for their device. I believe that based on the review of your device, it may be a candidate for de novo. Therefore, you may wish to make such a request of the Agency. For additional information on your options under section 513(f)(2), please refer to our guidance entitled, "New Section 513(f)(2) - Evaluation of Automatic Class II Designation, Guidance for Industry and Staff." This document is available at: www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm080195.htm.

Sponsor's *De Novo* Submission Should Include:

- Cover sheet identifying the submission as "Request for Evaluation of Automatic Class III Designation" or "*De Novo* Request"
- Risk/benefit analysis
- Classification (your recommendation based on risk analysis)
- Discussion of proposed controls that would be needed to assure the safety and effectiveness of the device
- The submission must be made in a manner compliant with eCopy or it will not be accepted. See the eCopy guidance at http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM313794.pdf

Sponsor's *De Novo* Petition Should Include:

Current Practice:

- 510(k) number on the NSE letter, if applicable
- Statement of cross reference to the information in the 510(k), if applicable

Proposed Guidance:

- Statement of cross reference to the information in the PDS and concurrently submitted 510(k)
- Summary of all changes since the PDS submission

Purpose of Controls

- Tools to manage risk
- Give assurance that risk posed by the device is reasonably low

Examples of General Controls for Class I Devices

Requirements (Regulations and statutes):

- To register and list
- That prohibit adulterated or misbranded devices
- That restrict sale and distribution or use
- That govern good manufacturing practices
- That provide for notification of risks and of repair, replacement, or refund

Examples of Class II Special Controls

If general controls are inadequate, then Class II Special Controls are also needed such as:

- Special Controls Guidance/Guideline Document
- Performance standards
- Special device labeling
- Postmarket surveillance/data

Class II Special Controls Guidance/Guideline Documents (SCGD)

- Must either:
  - Follow the mitigation measures identified in the special controls guidance/guideline or
  - Use alternative mitigation measures, but demonstrate to FDA's satisfaction that those alternative measures will provide at least an equivalent assurance of safety and effectiveness

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Class II Special Controls Guidance/Guideline Documents (SCGD)

- Agency Statement in Dental Devices: Reclassification of Temporary Mandibular Condyle Prosthesis Proposed Rule at 78 FR 9010
- This special controls guideline reflects changes the Agency is making to clarify its position on the binding nature of special controls. The changes include referring to the document as a “guideline,” as that term is used in section 513(a) of the FD&C Act, which the Secretary has developed and disseminated to provide a reasonable assurance of safety and effectiveness for class II devices, and not a “guidance,” as that term is used in 21 CFR 10.115. The guideline also clarifies that firms will need either to (1) comply with the particular mitigation measures set forth in the special controls guideline or (2) use alternative mitigation measures, but demonstrate to the Agency's satisfaction that those alternative measures identified by the firm will provide at least an equivalent assurance of safety and effectiveness. Finally, the guideline uses mandatory language to emphasize that firms must comply with special controls to legally market their class II devices. These revisions do not represent a change in FDA's position about the binding effect of special controls, but rather are intended to address any possible confusion or misunderstanding.

FDA Review of the *De Novo* Submission

- Review the request
- Evaluate the risk
- Identify applicable general and, if applicable, special controls
- Classify the device
- Write the Approval Order

FDA Review of the *De Novo* Submission

Current Practice Post FDASIA:

- Content proposed as early as Pre-submission
- Focused administrative effort once *de novo* submission is provided
- 120 calendar days

Proposed in Guidance:

- Content proposed during Pre *De Novo* Submission
- Administrative tasks performed concurrent with 510 (k) review
- 60 day review cycles

FDA Final Action

- Signed Approval Order classifying the device (Class I or II).
- New device can be marketed subject to the general controls and any special controls
- Publish a notice in the Federal Register announcing the classification within 30 days after the approval order is issued.

Summary of FDA's Review

- *De novo* confirmation
- During 510(k)/*de novo* Submission Review
  - FDA Identifies deficiencies and ensures they are addressed
  - New product code identified
  - Special controls identified and language written that will implement them.
  - NSE letter issued if 510(k) submitted
- After review complete
  - Approval order or denial of the *de novo* request

De Novo Responsibilities for Sponsor:

- Sponsor has the option to recommend a classification
- The sponsor is responsible for providing an initial draft proposal for applicable special controls if they recommend the device be found class II and a description of how the special controls would provide a reasonable assurance of safety and effectiveness.
- Sponsor should provide information on risk and clinical utility to support a class I or II designation

De Novo Responsibilities for Sponsor:

- Sponsor should provide information that demonstrates safety and effectiveness
- Sponsor sends in the *de novo* submission requesting risk-based classification of the device

Advice

- Talk with FDA early in the process
- Utilize resources on OIVD web site
- Review available guidance documents
- Submit special control recommendations to FDA

Resources for *De Novo*

- Guidance document “New Section 513(f)(2) - Evaluation of Automatic Class III Designation” (Feb 19, 1998): http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm080197.pdf

- Draft Guidance: “*De Novo* Classification Process (Evaluation of Automatic Class III Designation)” (Oct 3, 2011): http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM273903.pdf

OIVD Website Resources

http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/default.htm

- Guidance documents
- Device advice
- 510(k) database
- OIVD phone and e-mail list