The De Novo Process: Making It Work

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Primary Discussion Topics

- DeNovo 510(k) Regulation
- DeNovo Pathways
- Recent DeNovo Clearances
- Interactive Review
- Making DeNovo work – a case study
  - Pre-SUB Meeting
  - Regulatory Pathway Defined
  - Submission and FDA Review
  - Lessons Learned

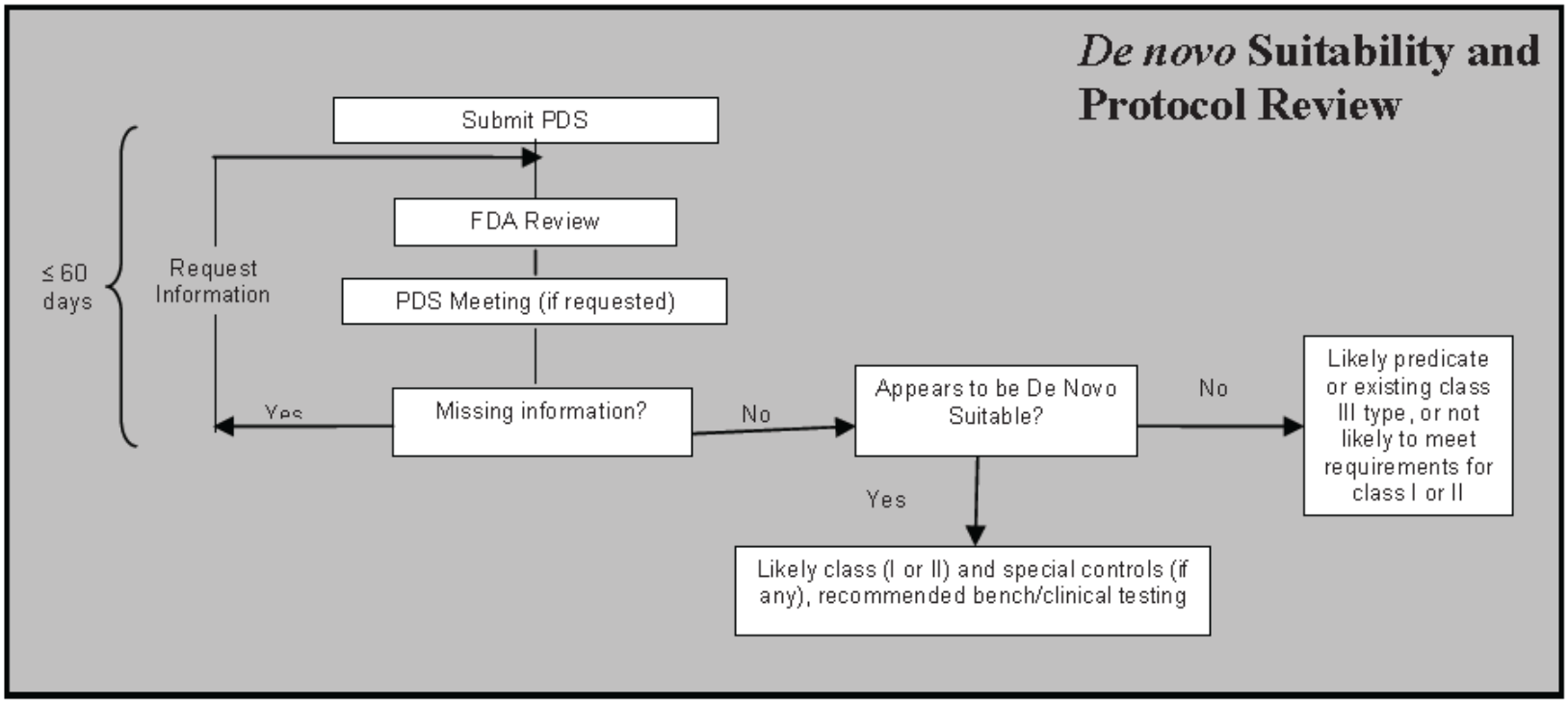
De Novo Regulation

- Section 513(f)(2) of the FDC Act
- Currently a very valuable pathway available to IVD developer
- Draft Guidance – October 3, 2011
- Low to Moderate Risk Devices
- Two different de novo pathways:
  - ✓ Direct/Pre-de Novo Submission
  - ✓ 510(k) NSE
- Practically speaking, FDA can decide this is the correct pathway prior to submission or during the review

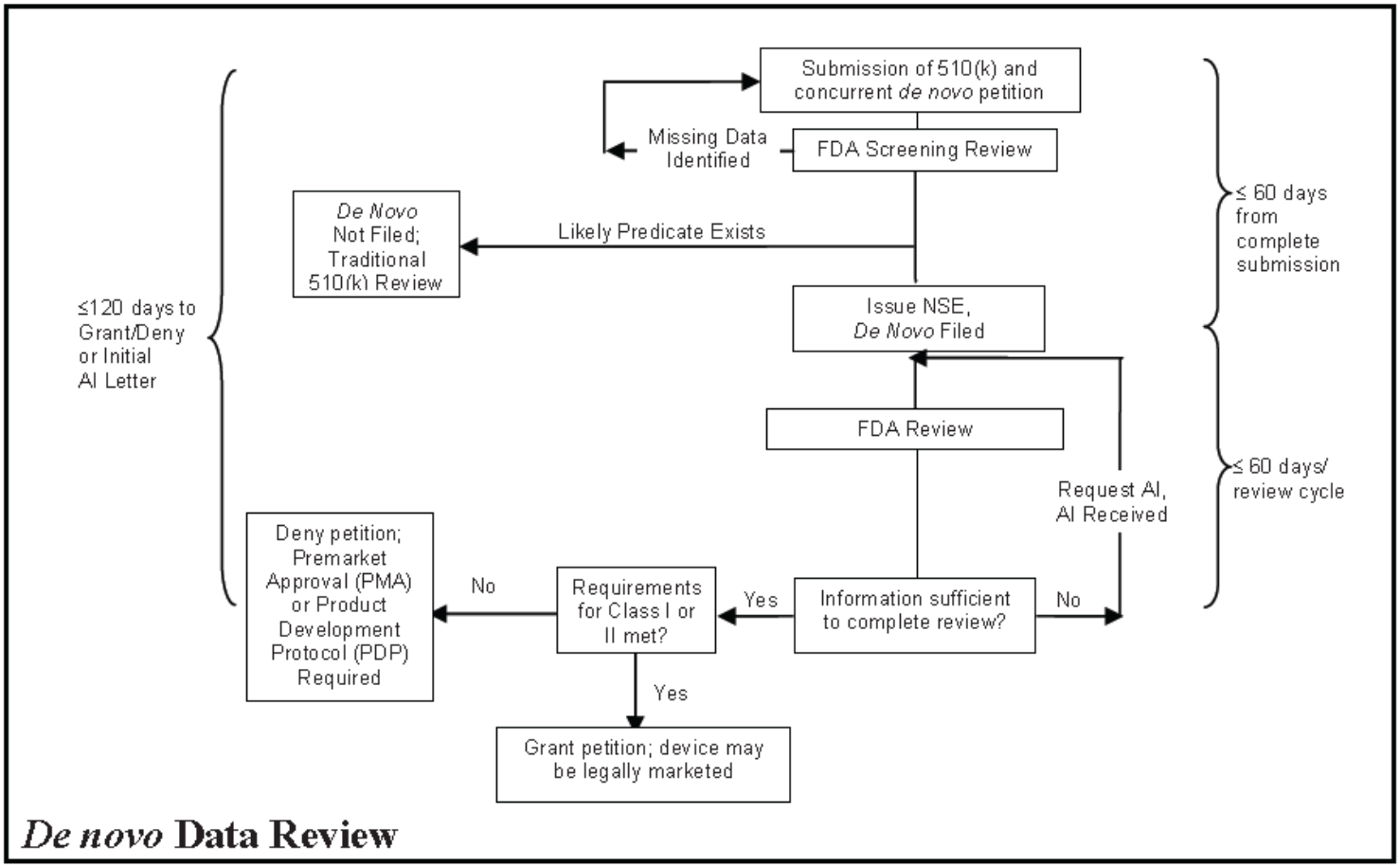
Types of De Novo Submissions

Direct – PDS followed by 510(k)/de novo pathway

Pathway initiated with a "pre *de novo* submission" (PDS)



Direct De Novo Pathway



Types of De Novo Submissions

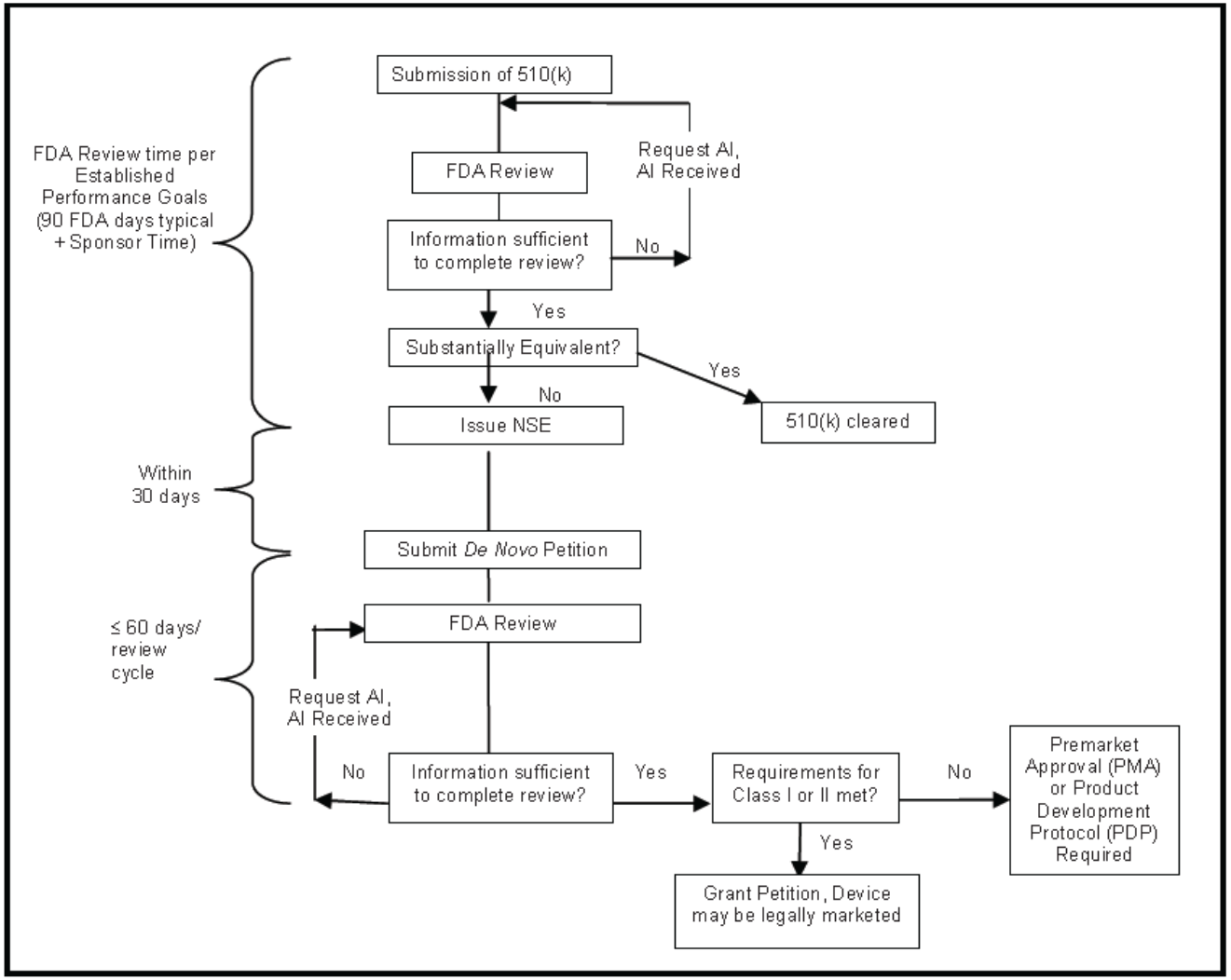
"***Traditional" Route*** *– Pathway initiated with a 510(k)*

- 510(k) NSE determination made citing no predicate – "automatic class III designation"
- Sponsor has 30 days to file a down classification petition
- Supported by data in the NSE 510(k) and a recommended Special Control (guidance document) mitigating risk associated with the device

Recent De Novo Clearances

- Microarray-based, genome-wide, postnatal chromosomal abnormality detection (K130313 1/17/2014)
- High throughput DNA sequence analyzer (K123989, 11/19/2013)
- Mass spectrometry, Maldi TOF, microorganism identification, cultured isolates (K124067, 8/21/2013)
- Nucleic acid-based, mycobacterium tuberculosis complex, resistance marker, direct specimen (K131706, 7/25/2013)
- Gastrointestinal pathogen panel multiplex nucleic acid-based assay system (K121454, 1/14/2013)
- Gram-positive bacteria and their resistance markers (K113450, 6/26/2012)

Traditional De Novo Pathway



Interactive Review

- February 28, 2008 CDRH/CBER Guidance
- 510(k)s, PMAs, and BLAs
- Authorized under MDUFMA II (2007)
- To assist in meeting performance goals
- Formalized interactive review process
- Encourage and facilitate communication between FDA staff and industry during premarket submission review

Interactive Review

More specifically,

- prevent unnecessary delays, reducing time to market;
- ensure FDA's concerns clearly communicated;
- minimize number of review cycles;
- minimize number of review questions conveyed through formal requests for additional information ("AI Letters");
- ensure timely responses from applicants

Interactive Review

Communication Tools

- Email
- Fax
- Phone calls
- Meetings
  - ✓ Teleconferences
  - ✓ Videoconferencing
  - ✓ Face-to-face
- Letters

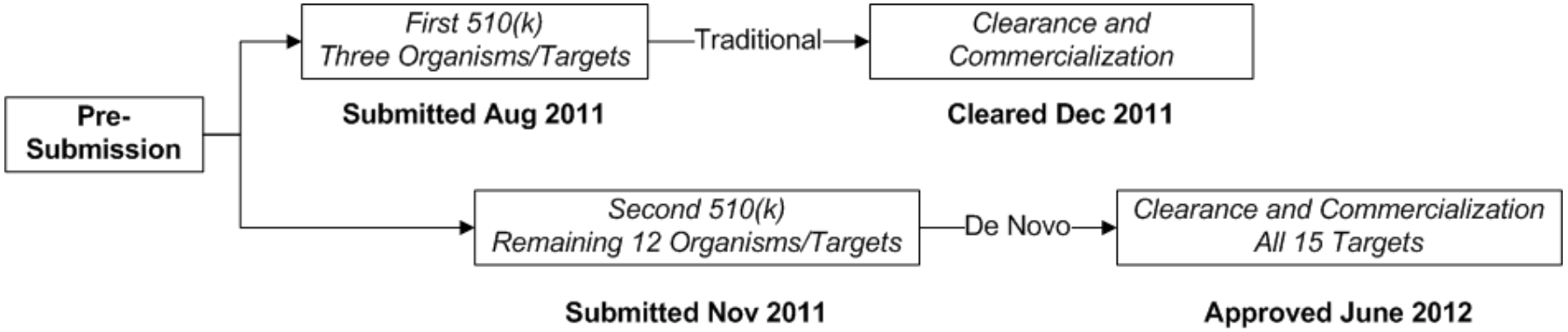
DeNovo Case Study

- 15-target Multiplex Molecular Microbiology device (Gram Positive Blood Culture)
- Detection and Identification of Bacterial Pathogens and Antimicrobial Resistance markers
- Positive Blood Culture Media
- 2.5 hour Assay Time
- Moderate-complexity Test

First Steps

- Pre-SUB (submission and response) – June/July 2010
  - ✓ Proposed Intended Use/Indications for Use
  - ✓ Analytical and Clinical Study Design
  - ✓ Proposed Predicate Device(s)
  - ✓ Anticipated Regulatory Pathway - based upon:
    - Existence of predicate devices for targets/organisms
    - Commercialization plan
- Regulatory Pathway Defined by FDA
  - ✓ Multiple 510(k) Submissions
  - ✓ DeNovo

Regulatory Pathway and Review Timeline



Interactive Review - Chronology

First 510(k) - Traditional

Action	Date	# days between responses	# Elapsed Days		"On the clock"	Initiator
			Per submission	Overall		
510(k) Submitted	Aug 19, 2011	-	-	-	-	CO
510(k) Received (official)	Aug 23, 2011	-	-	-	-	FDA
RFAI	Oct 5, 2011	43	43	43	Y	FDA
RFAI Response #1	Oct 12, 2011	7	50	50	Y	CO
AI Letter	Oct 13, 2011	1	51	51	Y	FDA
RFAI Response #2	Nov 1, 2011	19	70	70	N	CO
RFAI Response #3	Dec 2, 2011	31	101	101	N	CO
RFAI Response #4 (PI)	Dec 12, 2011	10	111	111	N	CO
Formal Response	Dec 14, 2011	2	113	113	Y	CO
Clearance Letter	Dec 16, 2011	2	115	115	-	FDA

Review Timeline – First Submission

Highlights

- Time to Clearance – 4 months
- Time to Receipt of 1st Review Questions – 43 days
- Time to Hold (formal AI Letter) – 51 days
- Average FDA/Sponsor Response Time during Interactive Review – ~15 days

Interactive Review - Chronology

Second 510(k) – De Novo

Action	Date	# days between responses	# Elapsed Days		"On the clock"	Initiator
			Per submission	Overall		
510(k) Submitted	Nov 18,2011	-	-	-	-	CO
510(k) Received (official)	Nov 21, 2011	-	-	-	-	FDA
Regulatory Pathway Discussion	Dec 19, 2011	28	28	118	Y	FDA
Follow-up Contact	Jan 6, 2012	18	46	136	Y	FDA
AI Letter	Jan 10, 2012	4	50	140	Y	FDA
RFAI Response #1	Feb 1, 2012	22	72	162	N	CO
RFAI Response #2	Feb 9, 2012	8	80	170	N	CO
Review Memo	Mar 6, 2012	26	106	196	N	FDA
RFAI Response #3	Mar 15, 2012	9	115	205	N	CO
RFAI Response #4	Apr 11, 2012	27	142	232	N	CO
RFAI Response #5	Apr 26, 2012	15	157	247	N	CO
RFAI Response #6	May 8, 2012	12	169	259	N	CO
RFAI Response #7	May 22, 2012	14	183	273	N	CO
RFAI Response #8 (PI)	May 25, 2012	3	186	276	N	CO
Formal Response	June 1, 2012	7	193	283	Y	CO
NSE Letter	June 11, 2012	10	203	293	Y	FDA
Down classification Petition	June 13, 2012	2	205	295	Y	CO
Approval Letter	June 26, 2012	13	218	308	Y	FDA

Review Timeline – 2nd Submission

Highlights

- Time to Receipt of 1st Review Questions – 28 days
- Time to Hold (formal AI Letter) – 50 days
- Average FDA/Sponsor Response Time during Interactive Review – approx 15 days
- Time to Clearance (2nd only) -approximately 6 months
- Overall Time to Clearance – approx 10 months

Lessons Learned

- Early collaboration meetings and on-going discussions with FDA prior to submission
- Use existing 510(k) and Decision Summaries to design validation studies
- Use pre-submission process to customize your multiplexed IVD validation testing
- Once submitted, keep the discussions going during the review
- Politely “nudge” your reviewer if you feel responses are taking too long and there may be something you can do to move it along

Lessons Learned

Incredibly important to be well organized during the interactive review; use of a “tracking system” highly recommended

Summary of RFAI Response Progress – Interactive Review Tracking
(K_____)

Topic	***FDA Question No.***	***Sponsor Action Taken / Proposed***	***Status*** *(Checked if complete)*	***OIVD Agreement/ Comments***	***Reference Page No.***
			☑		
			☐		

Lessons Learned

- Primary communication mode - *email*
- Easy to lose track of progress, particularly toward the end of the review when phone communication most often used
- Document all phone discussions in at least a bulleted email