Morgan Lewis

THE *DE NOVO* PATHWAY TO MARKET

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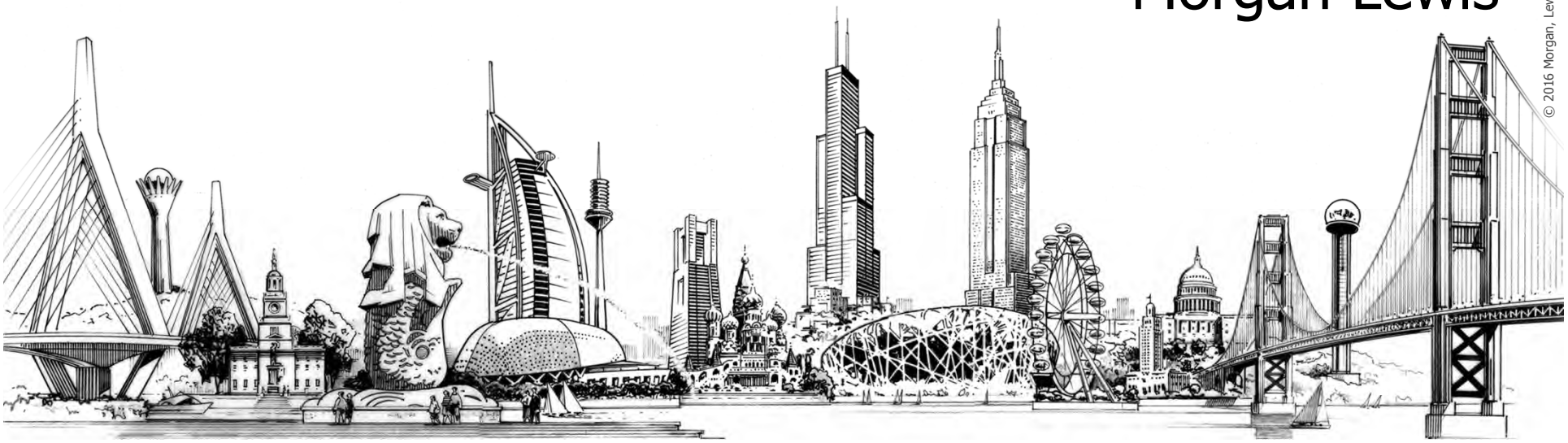


What Is a *De Novo* Submission?

- **"*De Novo*" pathway** -- Established by the Food and Drug Administration Modernization Act of 1997 to provide a new mechanism for reclassification of certain lower risk devices from class III to class I or II

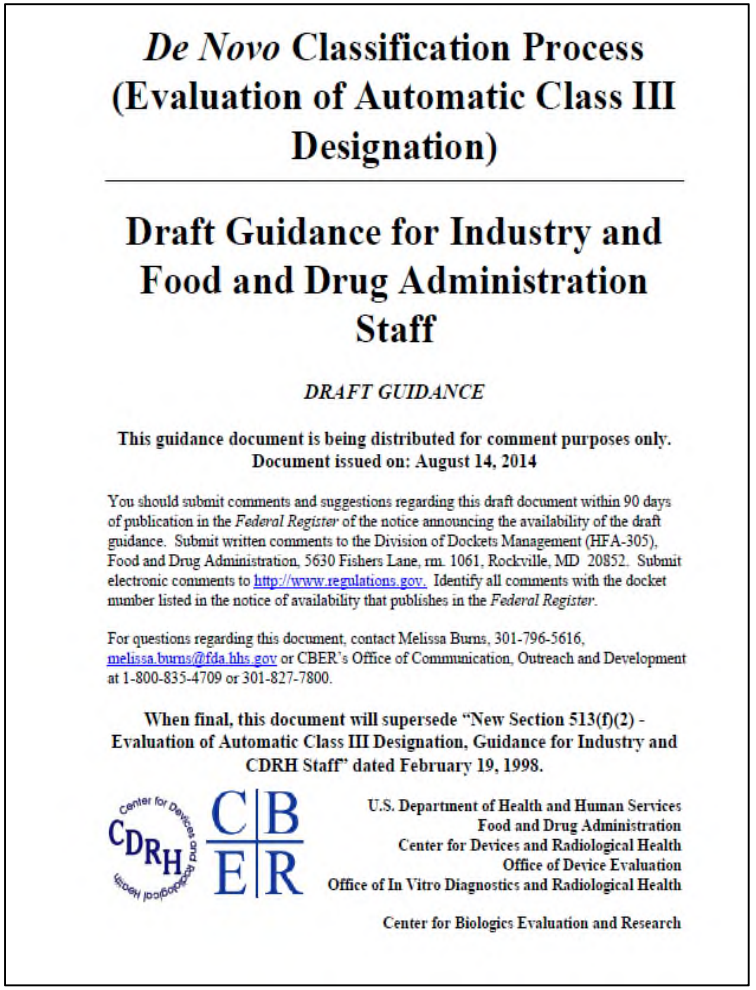
Section 513(f)(2) of the Federal Food, Drug, and Cosmetic Act (FD&C Act).

Background

- **Two step process** ("Post-NSE method")
  - Burdensome, lengthy process
  - Required a 510(k) to be filed and to be determined "not substantially equivalent" due to lack of a predicate device before *de novo* classification could be sought
- **"Direct" *de novo* pathway** – Food and Drug Administration Safety and Innovation Act of 2012 (FDASIA), created more streamlined alternative
  - Submission of a 510(k) and an NSE decision prior to submission of a *de novo* not required

FDA Guidance

- **Draft guidance** -- Draft guidance on the new *de novo* process issued in 2014, but never issued in final
- **New guidance?** -- In proposed performance goals under the Medical Device User Fee Act for FY 2018 - 2022, FDA commits to issue a draft and final guidance that includes a submission checklist to facilitate the review process



***De Novo* Classification Process (Evaluation of Automatic Class III Designation)**

Draft Guidance for Industry and Food and Drug Administration Staff

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.
Document issued on: August 14, 2014

You should submit comments and suggestions regarding this draft document within 90 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. Submit electronic comments to http://www.regulations.gov. Identify all comments with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this document, contact Melissa Burns, 301-796-5616, melissa.burns@fda.hhs.gov or CBER's Office of Communication, Outreach and Development at 1-800-835-4709 or 301-827-7800.

When final, this document will supersede "New Section 513(f)(2) - Evaluation of Automatic Class III Designation, Guidance for Industry and CDRH Staff" dated February 19, 1998.

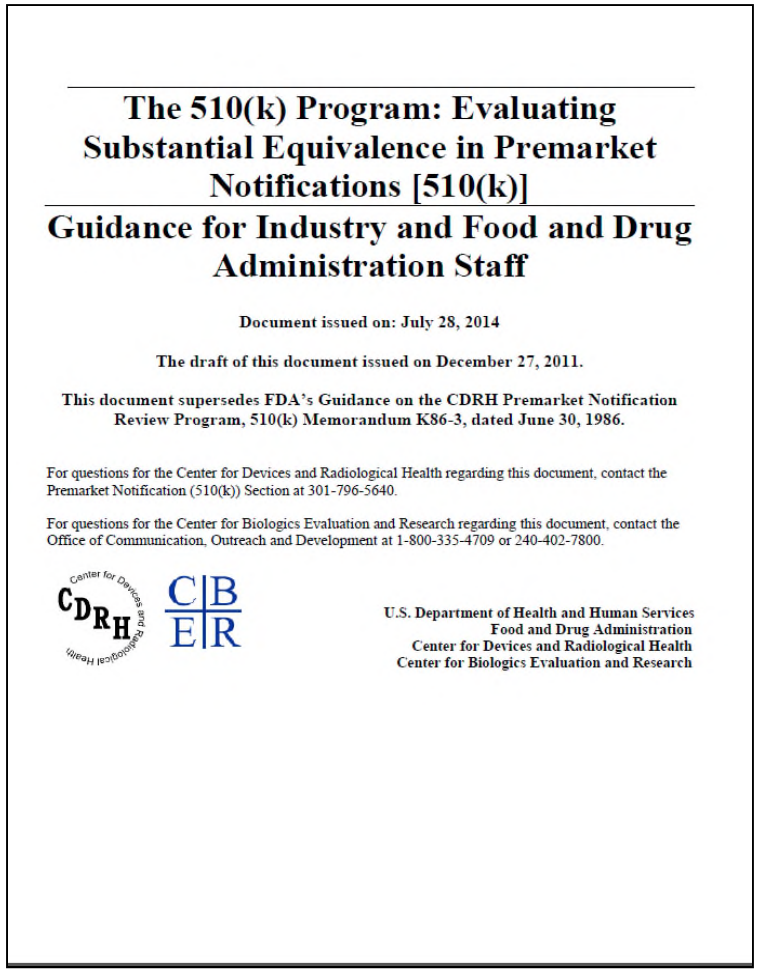
U.S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health
Office of Device Evaluation
Office of In Vitro Diagnostics and Radiological Health

Center for Biologics Evaluation and Research

When the *De Novo* Process May Be Used

- Criteria for the *de novo* process:
  - Novel devices that are Class III "by default"
  - Low to moderate risk devices
    - General controls or general and special controls would provide reasonable assurance of safety and effectiveness
    - Known benefits and risks of device are sufficiently understood; known risks can be effectively mitigated
- The *de novo* reclassification process is <u>not</u> available for devices that have been formally classified by FDA as Class III

Factors Promoting the *De Novo* Process



The 510(k) Program: Evaluating Substantial Equivalence in Premarket Notifications [510(k)]

Guidance for Industry and Food and Drug Administration Staff

Document issued on: July 28, 2014

The draft of this document issued on December 27, 2011.

This document supersedes FDA's Guidance on the CDRH Premarket Notification Review Program, 510(k) Memorandum K86-3, dated June 30, 1986.

For questions for the Center for Devices and Radiological Health regarding this document, contact the Premarket Notification (510(k)) Section at 301-796-5640.

For questions for the Center for Biologics Evaluation and Research regarding this document, contact the Office of Communication, Outreach and Development at 1-800-335-4709 or 240-402-7800.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health
Center for Biologics Evaluation and Research

- Post-FDASIA, FDA encouraging industry to submit *de novo* requests
- 2014 Guidance on Substantial Equivalence
  - Restricts use of **multiple predicates**
  - Advises when changes in indications for use **result in a new intended use**
  - Advises when different technical characteristics **raise different questions of safety and effectiveness**

FDA Benefit-Risk Considerations for *De Novo* Classifications

- Factors FDA considers in assessing benefit-risk:
  - Extent of probable benefit
  - Extent of probable risk(s)/harm(s)
  - Uncertainty
  - Patient-reported outcomes
  - Characterization of disease/condition
  - Patient preference
  - Availability of alternative treatments/diagnostics

FDA, Factors to Consider When Making Benefit-Risk Determinations in Medical Device Premarket Approval and *De Novo* Classifications (Aug. 24, 2016).

Examples of *De Novos* Granted for Devices Presenting More Than Low Risk

De novo pathway is not just for low risk devices --

- Neurovascular mechanical thrombectomy device for acute ischemic stroke (DEN150049)
- High intensity ultrasound for prostate tissue ablation (DEN 150011)
- Assay for determination of procalcitonin in serum/plasma to aid in assessment of patients with suspected sepsis (DEN 150009)
- Esophageal thermal regulation device (DEN 140018)

FDA Reviewing Divisions for *De Novo* Submissions

- Most CDRH reviewing divisions have reviewed and granted *de novo* submissions
  - But, generally, not more than 5 per year (exception: Neurological and Physical Medicine)
- One reviewing division – Orthopedics – has not granted any *de novo* submissions
- Over the last three years, Division of Neurological and Physical Medicine Devices and Division of Reproductive, Gastro-Renal and Urological Devices have reviewed the most *de novo* submissions

FDA Reviewing Divisions for *De Novo* Requests Granted – ODE

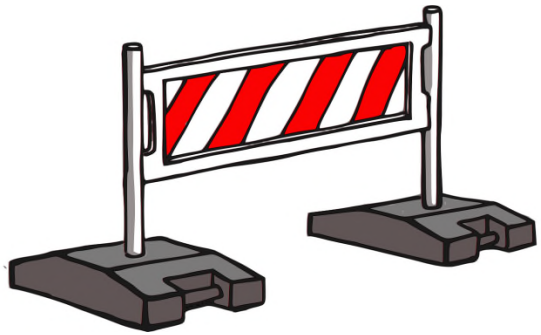
Calendar Year	CY 2013	CY 2014	CY 2015	CY 2016	Total
Cardiovascular	0	2	1	2	**5**
Neurological and Physical Medicine	4	7	1	5	**17**
Anesthesiology, General Hospital, Infection Control & Dental	1	2	1	1	**5**
Surgical Devices	1	2	2	3	**8**
Reproductive, Gastro-Renal, & Urological	2	4	5	4	**15**
Ophthalmic & ENT	0	0	3	4	**7**
Total	8	17	13	19	57

FDA Reviewing Divisions for *De Novo* Requests Granted – OIR

Calendar Year	CY 2013	CY 2014	CY 2015	CY 2016	Total
Chemistry/Toxicology	4	2	1	1	**8**
Microbiology	3	5	1	4	**13**
Molecular Genetics & Pathology	0	0	0	1	**1**
Immunology & Hematology	1	3	2	1	**7**
Radiology	2	1	1	0	**4**
Total	10	11	5	7	33

Pros of the *De Novo* Process

- Enables companies to bring more innovative low risk products to market, or to make new claims (i.e., new intended use) for existing Class I or II products, without having to go through the more rigorous premarket approval process
- Can establish limited barriers to entry to competitors through special controls and classification regulation
- Currently no user fee, but this will change under MDUFA IV
- Not a PMA
- May be the only alternative



Cons of the *De Novo* Process

- Statute states that *de novo* classification decisions to occur within 120 days
  - But no statutory timeline enforced against the FDA due to lack of user fees
  - Significant percentage of *de novo* submissions take much longer than 120 days
- Uncertainty and variability of data requirements
  - Clinical data may be required and, in some cases, the amount of data may approach that required to support a PMA
- Establishment of a new product code can facilitate 510(k) filings by competitors, and more expeditious market clearance
- User fees under MDUFA IV will be significant

Timing Issues – History

Fiscal Year	Number of *de novo* submissions	Number of *de novo* requests granted	Avg. total days to decision – Direct	Avg. total days to decision – Post-NSE
FY 2013	46	25	263 days	249 days
FY 2014	42	23	294 days	170 days
FY 2015	59	21	249 days	115 days
FY 2016	54	25	133 days*	101 days*

*Average review times for FY 2016 expected to increase as more *de novo* requests submitted in FY 2016 are cleared.

Timing Issues – Current Status

- In CY 2015 and CY 2016:
  - 2 submissions took 600 days or more
  - 4 submissions took between 300 and 400 days
  - 4 submissions took between 200 and 300 days
- Currently, about 40% of de novo submissions are reviewed in 150 days

Timing Issues – MDUFA IV Draft Commitments

- Per its draft MDUFA IV commitment letter, FDA's objective is to progress towards issuing a MDUFA decision within 150 FDA days of receipt for 70% of *de novo* submissions:

Submission Type	Action	FDA Review Days	Percent of Submissions to Meet FDA Days				
			FY18	FY19	FY20	FY21	FY22
De Novos	Decision	150	50%	55%	60%	65%	70%

- If a final decision is not rendered within 180 FDA days, FDA will discuss with the applicant all outstanding issues preventing the FDA from reaching a decision
- Congress has not yet reauthorized MDUFA

Data and Review Requirements

- Of 26 *de novo* applications granted in CY 2016, approximately:
  - 4 required a prospective clinical study
  - 13 required clinical performance data
  - 3 required a usability study/assessment

Data and Review Requirements

- Two *de novo* submissions have required or are scheduled for advisory panel review:
  - SEEKER Newborn Screening System (DEN 150035)
    - Intended for use in diagnosing lyosomal storage disorder
    - Reviewed by the Clinical Chemistry and Toxicology Devices Panel in August 2016
    - Granted on February 3, 2017 (submitted on Aug. 5, 2015)
  - Sentinel Cerebral Protection System (DEN160043)
    - An embolic protection device intended for use in transcatheter aortic valve replacement procedures
    - Circulatory System Devices Panel meeting scheduled for Feb. 23, 2017
    - Still pending (submitted on Sept. 20, 2016)

Follow-on 510(k)s

- Review time for follow-on 510(k)s often significantly lower, but few follow-on submissions

De Novo Submission (Sponsor)	Description of Device	Date De Novo Cleared/ Review Time	Follow-on 510(k)s	Date 510(k) Cleared/ Review Time
150049 Trevo ProVue Retriever (Concentric Medical)	Neurovascular mechanical thrombectomy device for acute ischemic stroke)	9/2/16 - 312 days	K162539	11/10/16 - 59 days
150058 Amplichek (Bio-Rad Labs)	Qualitative detection of MRSA, S. aureus, C. difficile, and VRE	3/28/16 - 101 days	K161573	9/2/16 - 87 days
150009 B.R.A.H.M.S. PCT sensitive KRYPTOR (B.R.A.H.M.S.)	Determines procalcitonin in serum/plasma to assess progression to severe sepsis and septic shock	2/20/16 - 353 days	K160911 K160729	6/28/16 - 88 days 6/13/16 - 90 days
150001 Relizorb (Alcresta, Inc.)	Enzyme packed cartridge to hydrolyze fat in enteral formula	11/20/15 – 322 days	K161247	6/30/16 - 58 days
150011 Sonablate (Sonacare)	High intensity ultrasound for prostate tissue ablation	10/9/15 - 200 days	K160942 K153023	11/14/16 -37 days (filed by de novo sponsor) 11/6/15 -22 days

Follow-on 510(k)s and Special Controls

- Special controls may help level the playing field for follow-on products:
  - Clinical data
    - Prospective study
    - Clinical performance testing
    - Usability studies
  - Non-clinical performance data
  - Animal (*in vivo*) testing
  - Software validation, verification, and hazard analysis
  - Labeling
  - Training

MDUFA IV Proposed User Fees

- *De novo* user fees proposed under MDUFA IV will be significantly higher than 510(k) user fees

Fiscal Year/ Submission Type	PMA	510(k)	*De Novo* (standard)	*De Novo* (small business)
FY 2018	$294,000	$9,996	$88,200	$22,050
FY 2019	$300,000	$10,200	$90,000	$22,500
FY 2020	$310,000	$10,540	$93,000	$23,250
FY 2021	$328,000	$11,152	$98,400	$24,600
FY 2022	$329,000	$11,186	$98,700	$24,675

Consideration of Pre-Submission Process Prior to Filing a *De Novo* Submission

- FDA recommends a pre-submission meeting/teleconference prior to filing a *de novo* submission. Factors to consider in deciding whether to request a pre-submission meeting include:
  - Suitability
  - Timing
  - Data requirements
  - Special controls

Recommended Content of a *De Novo* Submission

- To date, FDA has only issued draft guidance setting forth content requirements for a *de novo* submission, and thus FDA cannot describe these as requirements. As a practical matter, however, *de novo* submissions should include:
  - Administrative information
  - Regulatory history
  - Device information and summary
  - Change summary (if appropriate) (any changes made to device or proposed changes)

Recommended Content of a *De Novo* Submission

- *De Novo* submission content (cont'd):
  - Classification summary (rationale for why the device is different from any identified regulations, product codes)
  - Classification recommendation
  - Proposed special controls (for Class II devices)
  - Supporting protocols and/or data
  - Summary of benefits
  - Summary of known and potential risks to health
  - Risk and mitigation information (correlate each risk with a mitigation)
  - Benefit-risk considerations
  - Proposed device labeling

What Happens After a *De Novo* is Granted?

- Device may be legally marketed subject to the applicable general and special controls
- FDA will post an order announcing the new classification and controls, and will subsequently publish this in the Federal Register
- FDA will post a decision summary

THANK YOU