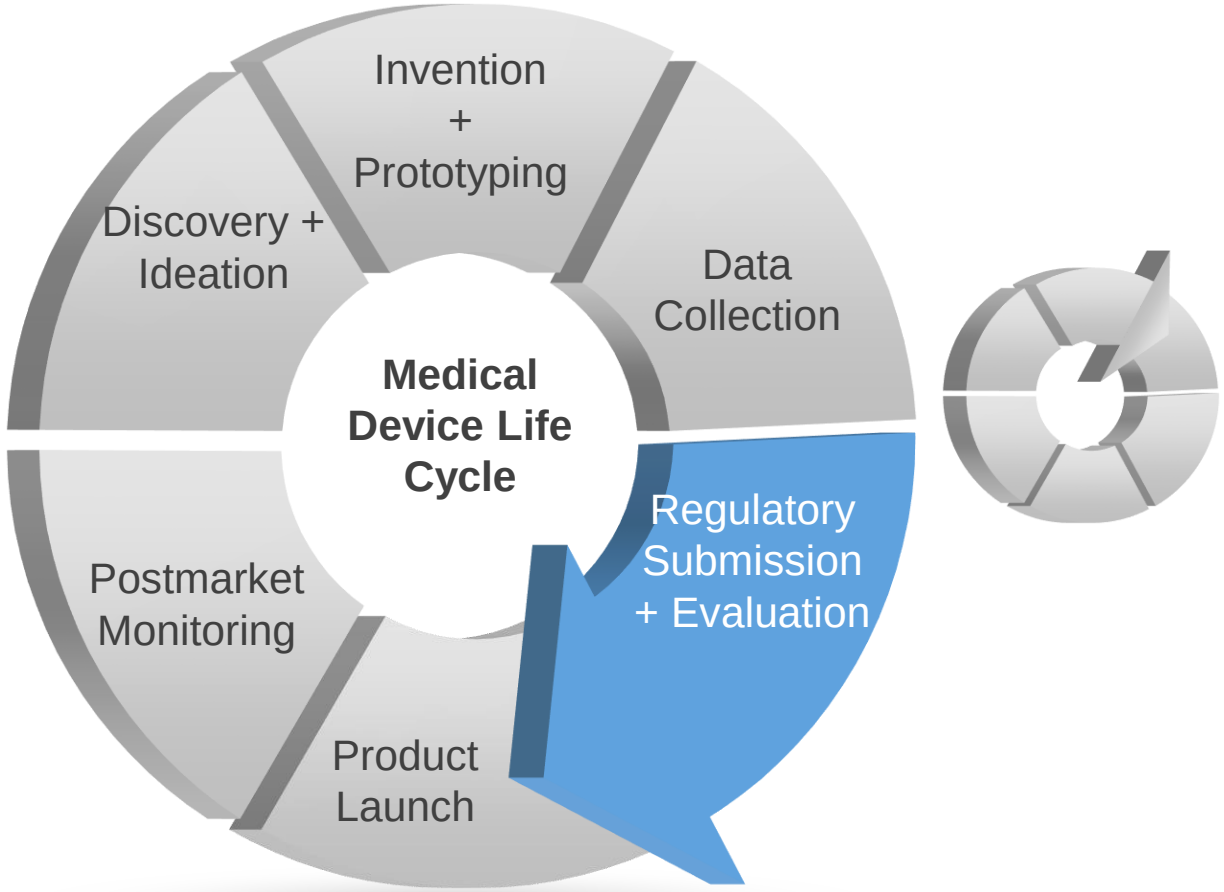
# Approval and Clearance Pathways for Medical Devices

Allyson B. Mullen
Hyman, Phelps & McNamara, P.C.
amullen@hpm.com
November 19, 2020

FDLI

# Submitting to FDA is one phase in the life cycle of a medical device






FDLI

# Overview

- All new devices need to be reviewed by FDA before they can enter the U.S. market, unless exempt
  - Important to understand which pathway is appropriate for a product type
- Multiple paths to the market
  - 510(k) premarket notification
  - Premarket Approval Application (PMA)
  - De Novo authorization
  - Emergency Use Authorization
- Applicant does not need to be a manufacturer
- Laboratory Developed Tests are unique

# What is a device?



FDLI

# Device Definition

- An “instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article…which is”
  - Recognized in the National Formulary or United States Pharmacopeia;
  - Intended for use in “diagnosis…or in the cure, mitigation, treatment, or prevention of disease”; OR
  - “[I]ntended to affect the structure or any function of the body of man or other animals, and which does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of its primary intended purposes”
  - FDCA § 201(h); 21 USC § 321(h) (Emphasis added).
- Includes a huge range of products – contact lenses, stents, software, in vitro diagnostic reagents and tests



FDLI

# Intended Use

- *Intended uses* refers to the objective intent of the persons legally responsible for the labeling of devices.
- The intent is determined by such persons' expressions or may be shown by the circumstances surrounding the distribution of the article.
- For example, by labeling claims, advertising matter, or oral or written statements by such persons or their representatives.
- It may be shown by the circumstances that the article is, with the knowledge of such persons or their representatives, offered and used for a purpose for which it is neither labeled nor advertised. . . . if a manufacturer knows, or has knowledge of facts that would give him notice that a device introduced into interstate commerce by him is to be used for conditions, purposes, or uses other than the ones for which he offers it, he is required to provide adequate labeling for such a device which accords with such other uses to which the article is to be put. 21 C.F.R. § 801.4 (Emphasis added).

# Importance of Intended Use

- A key regulatory concept
- The determination of whether a product is a device or a non-device (consumer product) hinges on the intended use of the product
- Intended use can be based on oral statements by employees or agents, such as
  - Sales calls
  - Site training on use of instruments
  - Trade shows
  - Speeches by sales reps
  - Reprints
  - Technical posters
- Intended use can be affected by statements by third parties that are referenced or used by or on behalf of the manufacturer

# Intended Use of a Stick

| Statements suggesting Popsicle Stick | Statements suggesting Pediatric Tongue Depressor |
|---|---|
| It's a popsicle stick | It's a Pediatric Tongue Depressor |
| Sterilized to food grade | Sterilized to medical grade |
| Kids love it | Young Patients love it |
| Makes popsicles last longer | Narrow enough to access those hard to reach places in kids' mouth |
| Tastes great | Tastes great |



FDLI

# Device v Consumer Product

- Cotton balls and swabs (“Q-tip”)
  - Consumer product:  For applying make-up
  - Device:  Applying medication to a body surface or collecting body fluids
- Exercise equipment
  - Consumer product: For general health and fitness
  - Device: For rehabilitation of injuries
- Cell Phone/Mobile Apps
  - Consumer product: For communication purposes
  - Device: For use as a stethoscope

# Identifying Appropriate Premarket Review Pathway



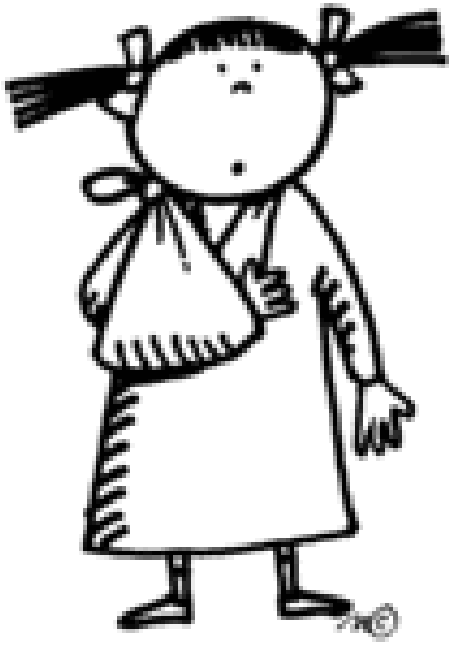
FDLI

# Risk Classification

- FDA uses a risk-based classification system for devices
- Class I – low risk
- Class II – moderate risk
- Class III – high risk

# Class I Devices

- Low risk devices
  - Not intended to be used in supporting or sustaining life
  - Not intended to be of importance in preventing impairment to human life; and
  - May not present an unreasonable risk of illness or injury
- Most class I devices do not require any FDA premarket submission (i.e., 510(k)-exempt)



# Class I Device Examples

- Manual stethoscopes
- Tongue depressors
- Arm slings
- Bandages
- Handheld surgical instruments
- Nonelectric wheelchairs



FDLI

# Class II Devices

- Moderate risk devices
- Most, but not all, class II devices require FDA clearance of a 510(k) premarket notification
  - Must demonstrate that the device is “substantially equivalent” to a predicate device



FDLI

# Class II Device Examples

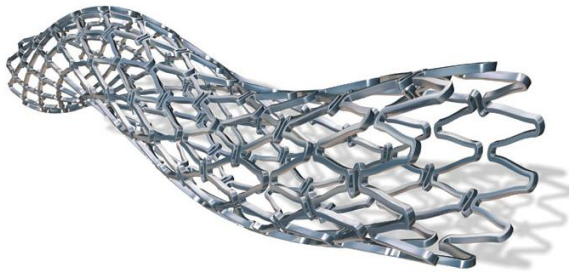
- Endoscopes
- Powered wheelchairs
- Infusion pumps
- Blood pressure cuffs
- Absorbable sutures
- Surgical gloves
- Syringes
- Contact lenses



FDLI

# Class III Devices

- Require Premarket Approval (PMA)
  - Required for high risk devices that pose a significant risk of illness or injury, or devices found not substantially equivalent to a predicate device through the 510(k) process, and where special controls cannot sufficiently mitigate the risks
  - PMA is more involved and costly than a 510(k)
  - Substantial administrative burdens both before and after approval
  - PMA must demonstrate reasonable assurance of safety and effectiveness



# Class III Device Examples

- Cardiac ablation catheters
- Coronary stents
- Breast implants
- Defibrillators
- Pacemakers
- Colorectal Cancer Screening Tests



FDLI

# Importance of Intended Use

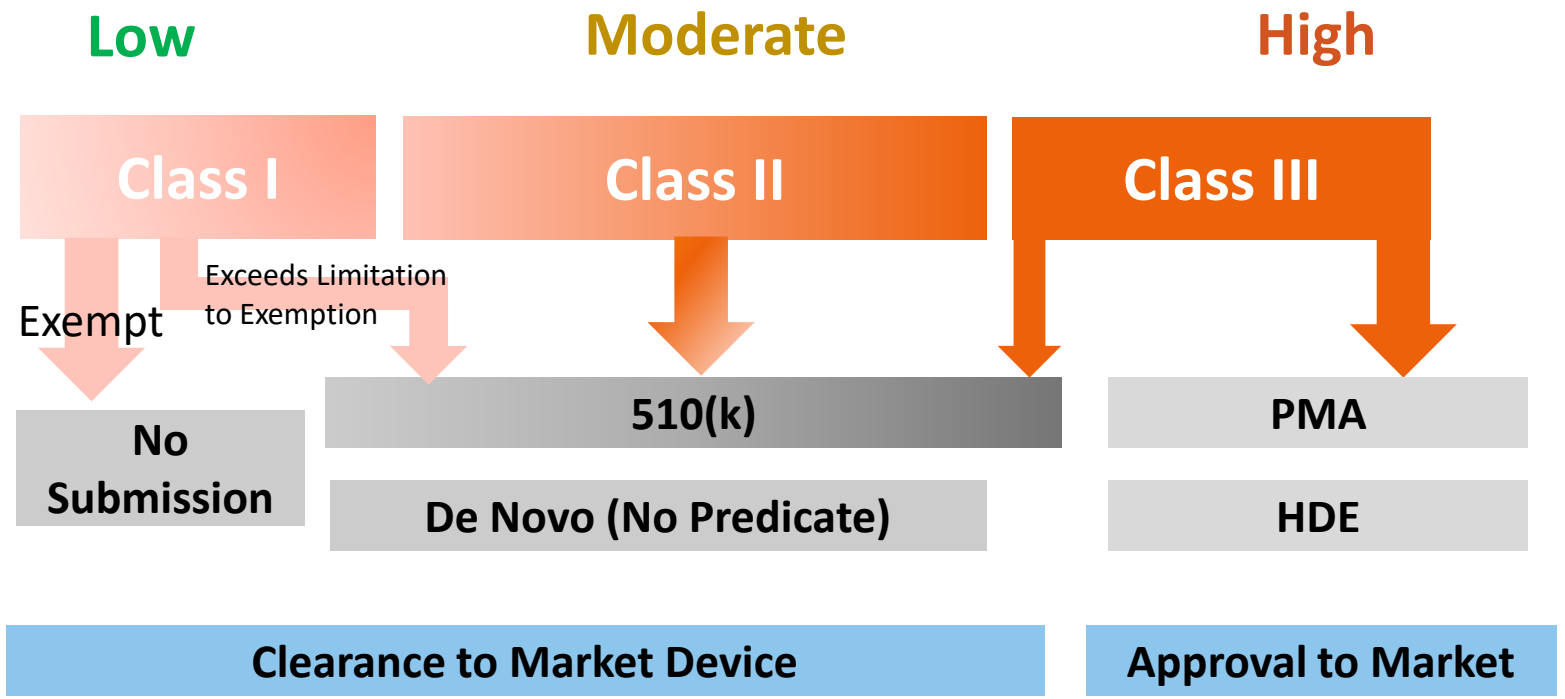
- The classification (class I, II, or III) hinges on the intended use of the device
- Communications by the company or its employees can change the intended use from what was originally cleared or approved by FDA
- Promoting the product for a new intended use can mean that a product exempt from the need for a 510(k) now needs a 510(k), or a 510(k) product needs a new 510(k) or a PMA

# Examples

BRCA1/BRCA2 Test:

- Class II – when intended to identify “if a woman is at increased risk of developing breast and ovarian cancer, and if a man is at increased risk of developing breast cancer or may be at increased risk of developing prostate cancer” (23andMe, DEN170046)
- Class III – when intended “as an aid in identifying ovarian cancer patients with deleterious or suspected deleterious germline BRCA variants eligible for treatment with Lynparza™ (olaparib)” (Myriad, P140020)

# Regulatory Pathways






FDLI

# Exempt Devices

- FDA has exempted many Class I and some Class II devices from the need for a 510(k)
- Classification regulations say whether type of device is exempt
- Exemptions no longer apply if the device “trips the limits” by using new technology or changing intended use, e.g., 21 C.F.R. § 870.9

# 510(k) Premarket Notification Pathway



FDLI

# 510(k)

- Primary route to market
  - More than 95% of new devices reviewed by FDA go through 510(k) process
- FDA receives ~3000 original 510(k)s per year
- Most 510(k)s are class II devices
- ~90% are successfully cleared
- Approximately 10% of 510(k)s include clinical data



FDLI

# 510(k) Requirements

- Need to show “substantial equivalence” to a “predicate device”
- A device is “substantially equivalent” to a “predicate” if it has:
  - The same intended use, AND
  - The same technological characteristics, OR
  - Different technological characteristics, but is
    - As safe and effective as the predicate, AND
    - Does not raise different questions of safety or effectiveness
  - 513(i) of the FD&C Act
- Interpreted by FDA in its Guidance Document “The 510(k) Program: Evaluating Substantial Equivalence in Premarket Notifications [510(k)],” July 28, 2014

# Predicate Device

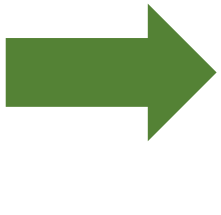
- Predicate device is a Class I or II device that has been cleared by a 510(k) by FDA or reclassified to Class I or II
- To simplify, “substantial equivalence” requires showing new device has same intended use and no new technological questions
  - Some latitude in applying definition
  - “Same intended use” does not necessarily mean word-for-word identical



FDLI

# Substantial Equivalence

= Predicate



- ✓ Same intended use
- ✓ Same technological characteristics

vs

- ✓ Same intended use
- ✓ Different technological characteristics do **not** raise different questions of safety and effectiveness and demonstrate the device is as safe and effective as the predicate



FDLI

# When is a 510(k) Required?

- For new devices prior to first introduction into the U.S. market
- Change in device or intended use may require new 510(k)
  - Significant change or modification to a device could necessitate a new 510(k).

# What constitutes significant changes or modifications that require a 510(k)?

The following constitute significant changes or modifications that require submission of a 510(k) Notice [21 CFR 807.81(a)(3)]:

(i) A change or modification in the device that could significantly affect the safety or effectiveness of the device, e.g., a significant change or modification in design, material, chemical composition, energy source, or manufacturing process

(ii) A major change or modification in the intended use of the device




FDLI

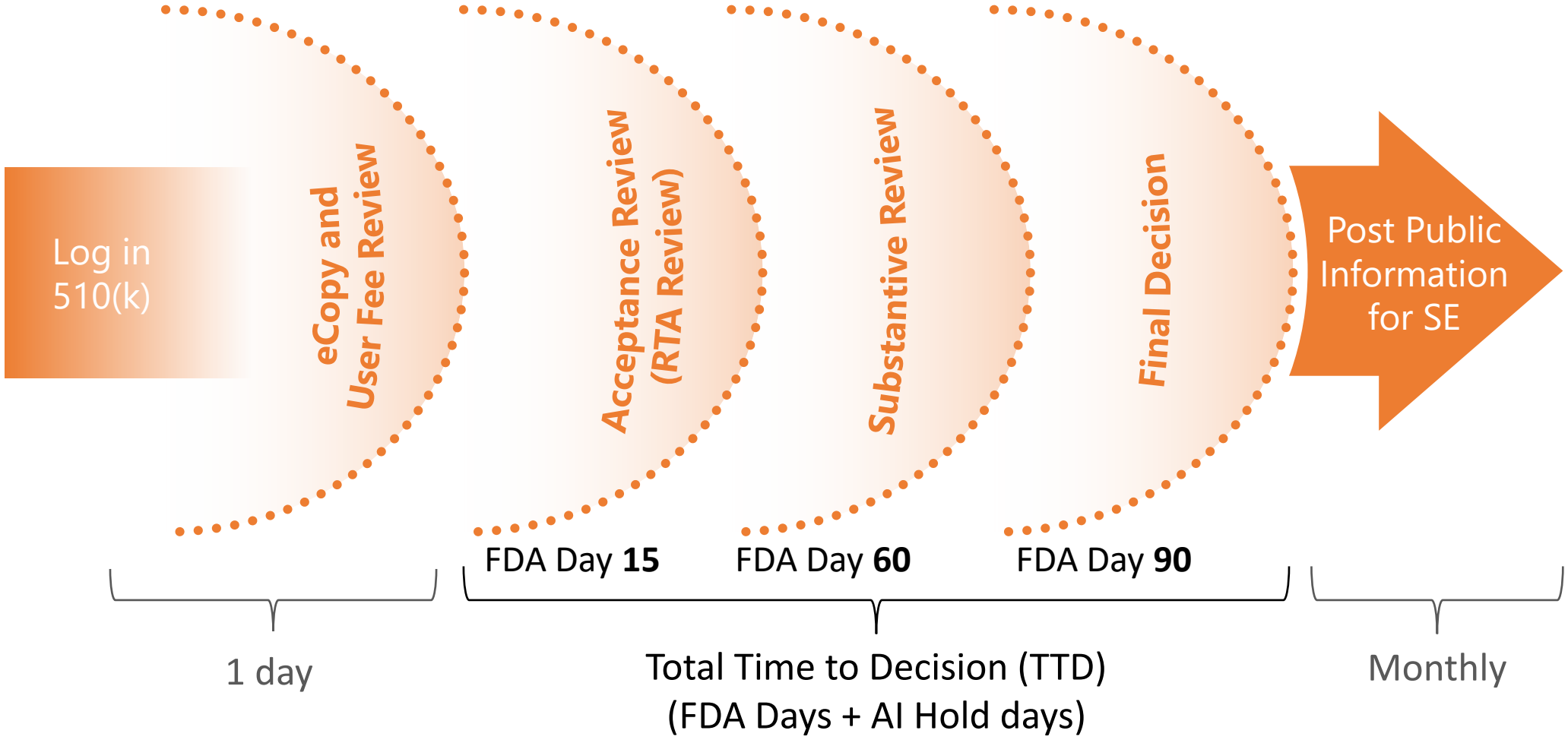
# 510(k) Requirements

- A 510(k) submission must contain, among other things:
  - a checklist
  - a device description;
  - draft labeling;
  - information; including data from testing, indicating how the device is similar to and/or different from a “predicate device”;
  - an Indications for Use Statement;
  - a 510(k) Summary or a 510(k) Statement; and
  - a “Truthful and Accurate Statement.”
- The 510(k) may also contain other information, such as data showing conformance to an FDA-recognized voluntary national/international standard; results from human clinical or animal testing
- Manufacturing information is not generally required in a 510(k)

# 510(k) – Technological Differences

- Verification and validation data required to support technological differences are safe and effective
- FDA considers patient perspective when there are technological differences between the proposed and predicate devices.
  - Perform a benefit-risk assessment that considers, among other things:
    - Characterization of the disease, including how the disease affects the patients
    - Patient tolerance for risk and perspective on benefit
    - Benefit for the healthcare professional, patient, or caregiver
- Benefit-Risk Factors to Consider When Determining Substantial Equivalence in Premarket Notifications (510(k)) with Different Technological Characteristics (Sept. 2018)

# The 510(k) review process




| TTD Goal | Fiscal Yr |
|---|---|
| 124 | 2018 |
| 120 | 2019 |
| 116 | 2020 |
| 112 | 2021 |
| 108 | 2022 |



FDLI

# A 510(k) can go on RTA hold for missing content

- FDA should only assess **presence** of critical elements, not the **adequacy** of those elements
- RTA decision will be communicated to the applicant within 15 days after receipt of valid eCopy and user fee
- Should receive copy of RTA checklist filled out by the reviewer – not a deficiency letter
- If not done within 15 days >> substantive review/interaction
- If rejected >> FDA clock stops and resets to day 0 when RTA response received
- Unlimited number of RTA cycles

# Two types of Additional Information (AI) requests

## Interactive Review Request

- The due date is ~ within 2-5 days of the requested date but negotiable
- Typically reserved for minor clarifications when asked before a hold
- Standard procedure for obtaining final clarifying information following a response to a hold
- No effect on review clock

## Hold/deficiency/AI Letter

- An automatic 180-day hold is granted – No need to send in an extension request every 30 days
- The maximum hold time is 180 days from the date of the hold
- Typically reserved for more complex issues that require more in-depth responses
- Review clock stops, restarts on DCC receipt of complete response



FDLI

# 510(k) Decision

- FDA can find device Substantially Equivalent
- FDA can find device Not Substantially Equivalent (NSE), i.e., reject
- Can appeal NSE decision and, maybe, AI letter

# 510(k) Myths

- 510(k)s not limited to “essentially identical” devices
- Not comparable to generic drug process
- Not a short cut or “loop hole”
- FDA can and does ask for testing data, including clinical data
- FDA can and does increase data requirements for newer versions of a device – do not assume that data that was sufficient for predicate will still be sufficient

# Pre-market approval (PMA)

# Pre-market approval (PMA)

- Highest risk devices
- Highest data requirements
  - Will always require clinical data and extensive other data
  - Voluminous submission
  - Need to include documentation showing compliance with Quality System Regulation
- 180-day FDA review clock
- Standard:  Reasonable assurances of safety and effectiveness

# PMA Process

- FDA will generally inspect manufacturing facility prior to approval
- FDA may audit clinical trial sites
- FDA may convene advisory panel, although rarely does any more
- FDA can impose post-approval requirements, e.g., post-approval studies
- Less flexibility in making changes than with 510(k) device
  - If there are significant changes in PMA-approved device or its claims, a PMA supplement is needed
- All subsequent devices for same intended use will need to submit a PMA

# PMA v 510(k)

| | 510(k) Submissions | PMA Applications |
|---|---|---|
| Type of devices | Class I, Class II | Class III |
| Standard of review | Substantial equivalence | Reasonable assurance of safety and effectiveness |
| Comparison to another device | Yes, comparison to a predicate device | No, device must stand on its own |
| FDA review timeframe | 90 FDA days | 180 FDA days |
| FDA determination | Clearance | Approval |
| Pre-clinical data required (animal, bench) | Generally yes | Yes |
| Clinical data required | Sometimes | Always |
| Pre-approval facility inspection required | No | Yes |
| User fee | $12,432 | $365,657 |

Bottom line: 510(k) process preferable



FDLI

# De Novo



FDLI

# De Novo Process

- A middle pathway between the 510(k) process and full blown premarket application (PMA) approval
- Intended for devices that utilize novel technologies that are not risky enough to justify regulation under the burdensome PMA process, but which lack a predicate device that would allow 510(k) clearance
- If a person believes the device is low to moderate risk but no appropriate predicate exists, the person may submit a *De Novo* without previously submitting a 510(k)
- Standard:  Data and information demonstrate that general controls or general and special controls are adequate to provide reasonable assurance of safety and effectiveness, and probable benefits outweigh probable risks

# De Novo Review Process

- Similar to 510(k)
- FDA is seeking to review approximately 50% in 150 FDA days
- Need to describe benefit-risk (in lieu of substantial equivalence)
- FDA will create new classification
  - Subsequent companies can submit a 510(k)
- FDA will establish "special controls" applicable to class of products, e.g., labeling, bench testing
- Other companies will be able to use *de novo* as a predicate device.
- Only one company can get *de novo* for category of device.

# Benefit-Risk Analysis

- For PMAs and de novos
- In March 2012, FDA issued a draft guidance document "to provide greater clarity for FDA reviewers and industry regarding the principal factors FDA considers when making benefit-risk determinations during the premarket review process" for devices subject to PMA or *de novo* review.

  New document: August 24, 2016
- Benefits
  - Type
  - Magnitude
  - Probability of receiving benefits
  - Duration

# Benefit-Risk Analysis

- Risks
  - Severity
    - Device-related
    - Procedure-related
  - Probability of harmful event
  - Duration of harmful event
  - Diagnostics: risk of false positive/negative

# Benefit-Risk Analysis

- Other factors
  - Uncertainty
  - Characterization of the disease
  - Patient tolerance/perspective
  - Alternatives
  - Risk mitigation
  - Novel technology addressing unmet need

# Benefit-Risk Analysis

- Patient Perspective
  - Patient perspective is not something that FDA has historically considered during PMA or *de novo* review.
  - The guidance contains substantial discussion of patient tolerance for risk as well as perspective on benefit.
    - Including the perspective on benefit demonstrates FDA's awareness that patients will not only consider risk in making their decisions about product use, but will also consider the benefits that may be achieved, despite the associated risk.
  - Risk tolerance will vary between patients.
  - Use of "patient-centered metrics."
  - By incorporating this discussion of patient tolerance for risk and perspective on benefit, FDA is recognizing that patients and practitioners should ultimately be responsible for determining whether a certain risk is acceptable for that particular patient in light of the potential benefits.

# Summary

- Device sponsors need to decide upon a regulatory pathway
- Access to that pathway can depend on claims and precedents
- Pre-submission process very helpful
- Do not assume that pathway to market will be simple or straightforward for new device

# Pre-Submission Program



FDLI

# Pre-Submission Program

- Pre-Subs include background information to FDA
- Key is to determine what questions to ask
- In a Pre-Sub, device manufacturers solicit specific feedback from FDA through directed questions
  - Provide description of device and information relevant to pivotal questions, e.g., suitability of clinical protocol, statistical plan, laboratory tests
- Topics/questions can include:
  - Regulatory strategy/pathway (e.g., 510(k) v. PMA, predicate device strategy)
  - Device design (e.g., intended use, new technology)
  - Clinical study (e.g., study design, number of subjects, sites, endpoints)
  - Non-clinical testing (e.g., type and/or design of tests)

# Pre-Submission Process (cont'd)

- If requested, meeting typically occurs 60 -75 days after submission
- FDA will provide written feedback approximately 5 days before the meeting
- Meeting should focus on areas of disagreement or clarifications, not concurrence
- Company can bring non-employees, including patient representatives
  - See draft guidance on patient engagement (September 2019)
- Sponsor submits draft minutes within 15 days to document meeting; FDA has 30 days to comment
- Pre-sub feedback is not binding on FDA, but process still extremely helpful
- Companies should use pre-sub process for any novel device

# Pre-Submission Example

- Company plans to use a new patient reported outcome measure as the primary endpoint in its clinical study.
  - Do you think a pre-submission would be useful?

# Pre-Submission Example

- Company plans to use a new patient reported outcome measure as the primary endpoint in its clinical study.
  - Do you think a pre-submission would be useful?
- **YES**. Questions might focus on:
  - Clinical study design
  - Prior validation of patient reported outcome measure to ensure FDA agreement as to its appropriateness in the clinical study design
  - Additional endpoints that may align with other similar devices (if any)

# Hypothetical

- Would you file a Pre-Sub for:
  a. A new type of glucose meter that measures an individual's glucose level using light measurements through the tissue as compared to current systems that measure glucose from a blood sample (finger prick).
  b. Laser ablation tool with a general 510(k) clearance for laser ablation of soft tissue. Your company wants to gain clearance for laser ablation of cardiac tissue. There are no devices cleared specifically for cardiac ablation.
  c. A new examination glove that is made from a novel high-strength polymer, not latex like other examination gloves.

# Emergency Use Authorization



FDLI

# What is an EUA?

- Emergency Use Authorization
- An authority granted to the FDA under sections of the Federal Food, Drug, and Cosmetic Act including by the Pandemic and All-Hazards Preparedness Reauthorization Act of 2013.
- It does not constitute approval of the device in the full statutory meaning of the term.
- Authorizes FDA to facilitate availability of an unapproved product, or an unapproved use of an approved product, during a declared state of emergency.
- Ultimately, the emergency will end, and companies will need to obtain 510(k)/De Novo.

# The PREP Act

- Public Readiness and Emergency Preparedness Act, Pub. L. 109-148, 119 Stat. 2818 (2005) (codified at 42 U.S.C. § 247d-6d).
- A "covered person" is immune from almost all liability relating to the use of a "covered countermeasure," which is defined to include a medical device that is "**authorized for emergency use** under Sections 564, 564A, or 564B of the [Federal Food, Drug, and Cosmetic Act (FDC Act)]."
- Preempts virtually any personal injury lawsuit arising from use of the EUA product, whether under federal or state laws
- Getting PREP Act protection is commercially very valuable.

# Why Does an EUA Matter?

- Because without it, companies do not have the liability immunity set forth in the PREP Act.
- FDA has allowed some diagnostic products to be sold with a notification and without an EUA – there is almost no market for this product.

# COVID-19 and FDA Guidance

- 24 COVID-19 related guidance documents for industry, FDA staff, and other stakeholders
- for COV32 Virtual Town Halls for Test Development and Validation
- ~70 FAQs on Testing ID-19
  - Laboratories and manufacturers offering tests for COVID-19
  - Testing supply
  - 3D printed swab
  - Test validation
  - COVID-19 Related test data and reporting
  - Clinical laboratory diagnostic test
  - Test kit manufacturer diagnostic test
  - Serology/antibody test

# FDA Exemptions

- Digital health devices for treating psychiatric disorders
- Remote digital pathology devices
- Imaging systems
- Non-invasive fetal and maternal monitoring devices used to support patient monitoring
- Telethermographic systems
- Extracorporeal membrane oxygenation and cardiopulmonary bypass devices
- Remote ophthalmic assessment and monitoring devices
- Infusion pumps and accessories

# COVID-10 and IVD Workload

- FDA has never faced a challenge like COVID-19
- IVDs have been in the forefront of the regulatory challenge
- FDA has granted over 270 IVD EUAs
  - At least 180 EUAs for molecular diagnostic tests kits
  - At least 35 EUAs for molecular LDTs
  - At least 5 EUAs for antigen test kits
  - At least 50 EUAs for serology tests
- Issued multiple policy statements
- Released numerous templates
- Held weekly Town Hall meetings
- Spillover effect on other IVDs:
  - Some companies with non-COVID IVDs have had their pre-submissions withdrawn
  - Companies were notified in-house IVD submissions were going on hold
  - Missing 510(k) deadlines

# Laboratory Developed Tests



FDLI

# LDT Background

- One of the most controversial device issues today
- Test developed and performed in a single laboratory
- Includes genetic tests, tests for rare conditions, and companion diagnostics
- Tens of thousands available, including many innovative tests
- Many are standard of care



FDLI

# Clinical Laboratory Improvement Amendments (CLIA)

- Federal statute under which clinical laboratories are regulated
- Comprehensive regulatory scheme for the federal oversight and certification of clinical laboratory testing procedures and methodologies
- Requirements for laboratory personnel and the documentation of procedures for individual clinical laboratory tests
- Mainly administered by Centers for Medicare & Medicaid Services

# FDA First Asserts Authority over LDTs in 1992

- August 3, 1992 draft Compliance Policy Guide entitled "Commercialization of Unapproved In Vitro Diagnostic Devices Labeled for Research and Investigation."
- Asserts that "laboratories have been manufacturing" LDTs "either from products already on the market, or from components, and utilizing these unapproved products for diagnostic purposes."
- LDTs are to be regulated "as any unapproved medical device."

# 1997 ASR Regulation

- Preamble of November 21, 1997, Final Rule relating to the Classification of ASRs
- “FDA believes that clinical laboratories that develop such [laboratory-developed] tests are acting as manufacturers of medical devices and are subject to FDA jurisdiction under the act. However, FDA recognizes that the use of [laboratory] developed tests has contributed to enhanced standards of medical care in many circumstances and that significant regulatory changes in this area could have negative effects on the public health. For these reasons, FDA declines to accept the suggestion that all [laboratory] developed tests be classified as Class II or III medical devices.”

# 1998 Denial of HPM Citizen Petition

- Our firm submitted citizen petition on Oct. 22, 1992 requesting that FDA not regulate LDTs as medical devices. Our firm argued that:
  - FDA regulation of LDTs was inconsistent with CLIA
  - FDA lacks statutory authority to regulate LDTs
  - FDA regulation of LDTs would undermine healthcare
  - FDA can only implement such a policy through notice-and-comment rulemaking
- FDA denied the citizen petition on Aug. 12, 1998

# Enforcement Discretion

- For years, FDA has taken the position that LDTs are medical devices but that it will generally exercise enforcement discretion
- Examples of enforcement
  - Warning Letter to LabCorp (Sept. 29, 2008)
  - Warning Letter to EXACT (Oct. 11, 2007)
  - Various Untitled Letters to various direct to consumer tests
  - Warning letter to 23andMe, Inc. (Nov. 2013)
  - August 2016 letter regarding ovarian cancer testing
  - 2019: Attack on pharmacogenomics – relationship between genes and drugs.

# 2010: FDA Announces Plan to More Actively Regulate LDTs

- FDA announced in June 2010 that it was revisiting this years-long policy of exercising enforcement discretion over LDTs
- FDA held a public workshop to discuss the issue in July 2010
- FDA officials subsequently indicated that agency was developing a plan to more actively regulate LDTs under a risk-based framework, to be issued for comment as guidance

# FDA Proposed Framework for Actively Regulating LDTs

- Food and Drug Administration Safety and Innovation Act required FDA to notify Congress at least 60 days before the agency issued a draft guidance document or regulation regarding LDTs
- July 31, 2014 – FDA provided Congress with Notice and copies of two draft guidance documents
- October 3, 2014– FDA formally issued two draft guidances with only minor changes in *Federal Register*

# Additional Challenges to FDA Statutory Authority

- Washington Legal Foundation's Sept. 2006 and American Clinical Laboratory Association (ACLA) June 2013 citizen petition challenge FDA authority to regulate LDTs
- On July 31, 2014, the same day as it provided notification to Congress, FDA rejected the WLF and ACLA petitions
- The American Clinical Laboratory Association retained two very prominent litigators to challenge FDA

# The End of LDT Regulation?

- November 2016: the Obama administration announced an end to plans to push ahead with LDT guidelines
- August 2020: the Department of Health and Human Services announced that FDA lacked the legal authority to regulate LDTs without issuing regulations
- October 2020: FDA stops reviewing EUAs from labs for LDTs for COVID tests
- November 2020: The election
- Will there be another reversal in policy?
- There has been talk for years of legislation; perhaps now it will move forward
  - If there is new legislation, it will cover all IVDs, not just LDTs

# Questions



FDLI