Overview of the FDA Submission Process

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FDA/CDRH/OIR/DIHD

NCI SBIR Workshop on Federal Resources to Accelerate Commercialization
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Office of Medical Products and Tobacco

- Center for Biologics Evaluation and Research (CBER)
- **Center for Devices and Radiological Health (CDRH)**
- Center for Drug Evaluation and Research (CDER)
- Center for Tobacco Products

Center for Devices and Radiological Health

- Office of Compliance
- Office of Device Evaluation (ODE)
- **Office of In Vitro Diagnostics and Radiological Health (OIR)**
- Office of Science and Engineering Laboratories
- Office of Surveillance and Biometrics

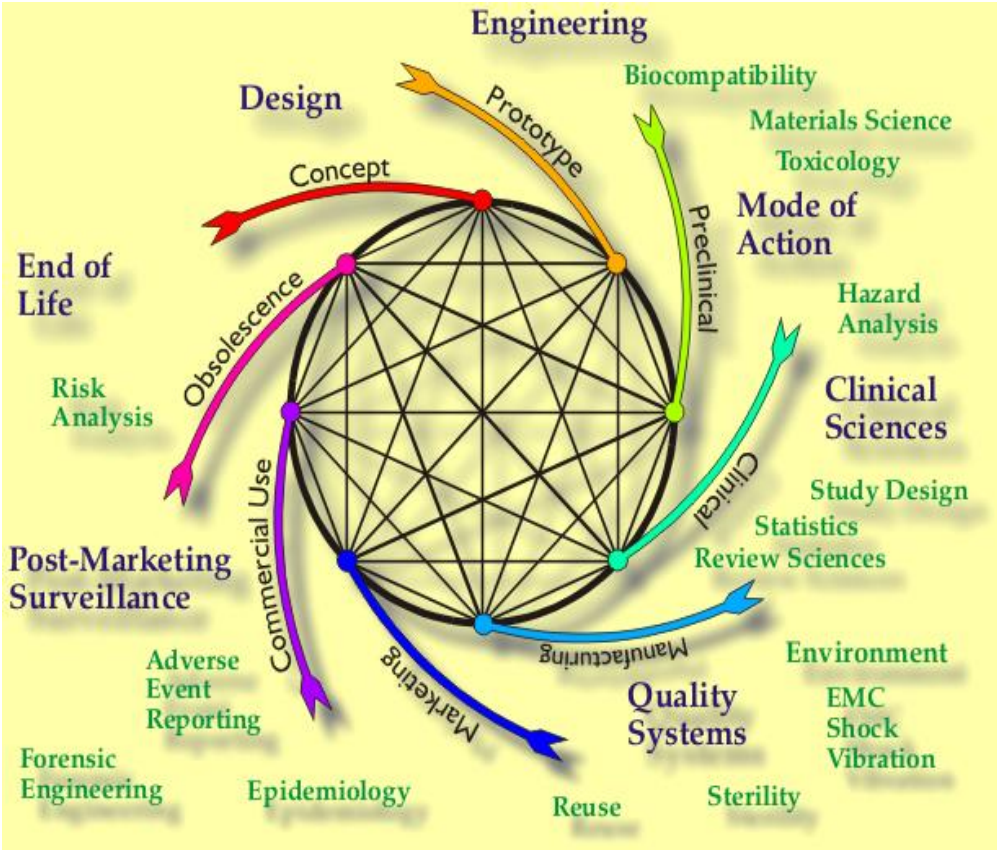
Office of In Vitro Diagnostics and Radiological Health (OIR)

- Division of Chemistry and Toxicology Devices
- **Division of Immunology and Hematology Devices**
- Division of Microbiology Devices
- Division of Radiological Health
- Division of Mammography Quality Standards
- Office of the Director (Personalized Medicine Staff)

http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDRH/CDRHOffices/ucm127854.htm#OIR

*FDA has Regulatory Authority over **All** Medical Devices*

- Manufacturing- (Quality Systems Regulations)
- Premarket Review
- Postmarket Surveillance
- Human subject protection



In vitro diagnostic products (IVD's) are:

- reagents, instruments, and systems used in diagnosis of disease or other conditions…
- in order to cure, mitigate, treat, or prevent disease…
- intended for use in the collection, preparation, and examination of specimens taken from the human body.

[21 CFR 809.3]

Types of Diagnostic Devices: IVDs

- Mostly **Assays**:

  Microbiology: infectious disease, antimicrobial susceptibility
  Immunology & Hematology: tumor markers, allergy, cancer dx
  Chemistry & Toxicology: pregnancy tests, newborn screening

- **Platform** is part of device
- Some **collection devices**
- **Software** and **diagnostic algorithms**

- Statutes and post-market regulation different from other CDRH devices

QSR – Quality System Regulations

- 21 CFR 820 ≈ ISO 9001

- Implementation of design controls to all elements of IVD:
  - designing, manufacturing, packaging, labeling, storing, installing, and servicing of all finished medical devices

- Manufacturer must:
  - identify both device inputs and outputs,
  - ensure verification of performance
  - establish validation of performance to predict and ensure proper use in the hands of the intended user

Pre-market Review of IVDs

- To evaluate safety and effectiveness….
- Driven by Intended Use….
  - Everything depends on IU!
- And Risk…
  - Risk based on harm from incorrect test result
  - Risk decides what kind of supporting information is needed

Basis of Device Review by FDA: "Safety and Effectiveness"

- **Safety**:
  - *Are there reasonable assurances, based on valid scientific evidence that probable benefits to health from use of the device outweigh any probable risks?*
- **Effectiveness:**
  - *Is there reasonable assurance based on valid scientific evidence that the use of the device in the target population will provide clinically significant results?*

Intended Use / Indications for Use

What the device is:

- Analyte that is measured
- The measurement principle of the test
- The specimen type

The context in which the device is used:

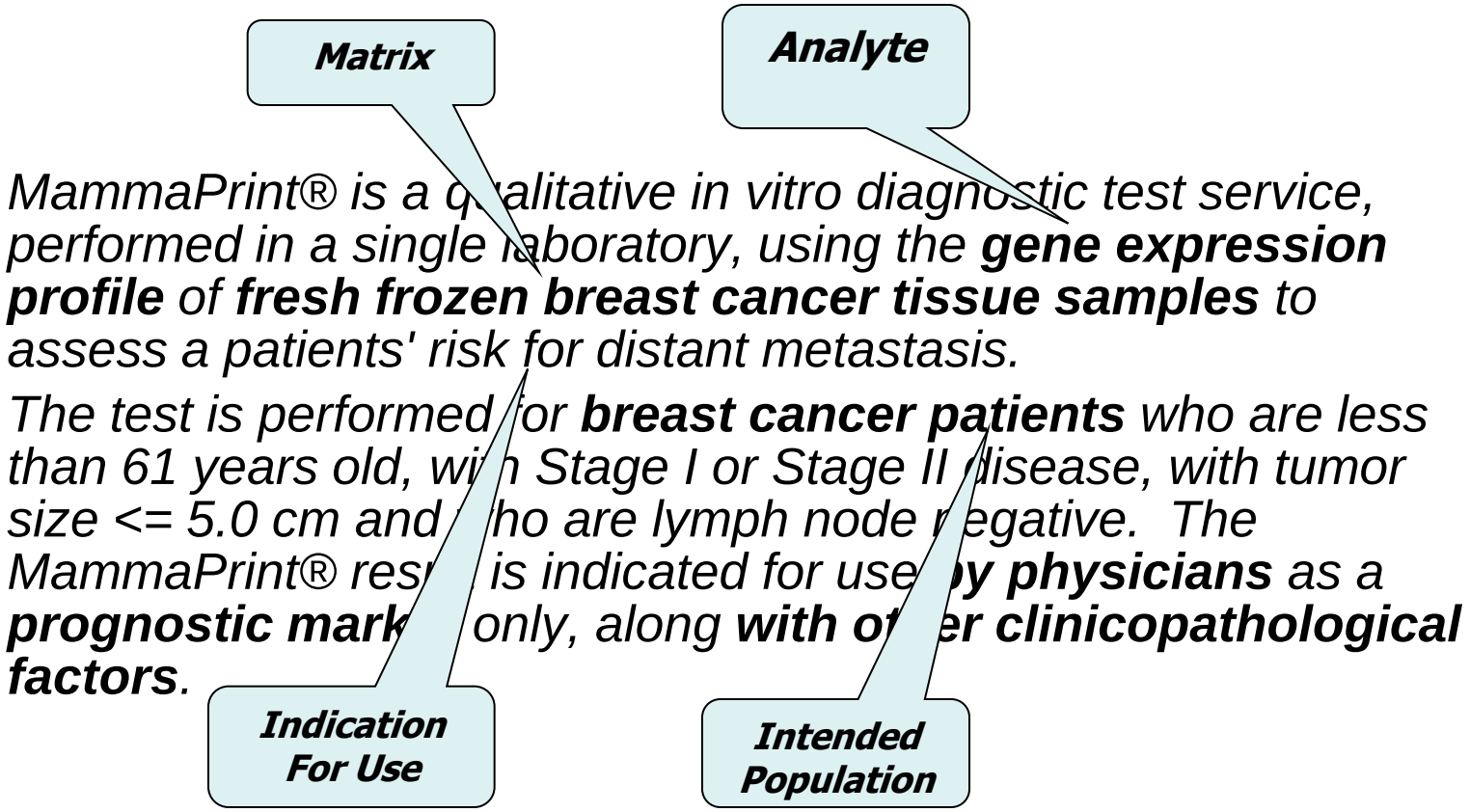
- The setting (clinical laboratory, point-of-care, etc.)
- Instrumentation required
- The target condition
- The clinical purpose (diagnosis, prognosis, monitoring)
- The target population for whom the test is intended

Intended Use / Indications for Use

- The “Intended Use” is driving force of entire pre-market process

- Claims made in IU must be supported by performance data

Intended use example



Risk depends on Intended Use:

- Level of OIR review and type of studies requested generally depend on the Intended Use claims, not technology or assay

- Prostate-specific antigen (PSA) testing:
  - Aid in detection of prostate cancer (class III, PMA)
  - Monitoring prostate cancer patients for disease progress (class II, 510(k))

- Alpha-fetoprotein (AFP) testing:
  - Prenatal screen for neural tube defects (class III, PMA)
  - Monitoring for testicular cancer (class II, 510(k))

Risk classification

- Class I: low risk
- Class II: moderate risk
- Class III: high risk

- Each risk class has its own standard of evidence….
  - and requirements for review

Device classification

	Class I	Class II		Class III
Risk	Low	Moderate		High
Clearance/ Approval	Not required	510(k)	Denovo Process	PMA
Controls	General	General +Special	General +Special	General +Special
Comparison	Not req'd	Predicate	Clin Truth	Clin Truth
Submission Studies	Not required	Preclinical +/-Clinical	Preclinical +Clinical	Preclinical +Clinical
	↓	↓	↓	↓
	Marketed	**Cleared**	**Granted**	**Approved**

Center for Devices and Radiological Health
CDRH

Regulatory controls are different

- **General Controls:** requirements to assure S&E tests
  - Facility registration (21 CFR 807.20)
  - Device listing (21 CFR 807.20)
  - QSR (21 CFR 820)
  - Labeling requirements (21 CFR 801 or 809)
- **Almost all IVDs require at least general controls**
- **Special Controls:** when general controls are not adequate for S&E:
  - special labeling requirements,
  - mandatory analytical and clinical performance standards
  - postmarket surveillance

Determining Risk for your device

- You have a new IVD……
- Is there a predicate?
- Is there a significant risk if test gives an incorrect result?
- Is there a risk associated with obtaining the specimen for testing?
- What's my intended use? Is the device used to:
  - diagnose significant disease (e.g. cancer)
  - or screen asymptomatic patients (cervical cytology)
  - or direct therapy (Her2 testing for administration of Herceptin)?

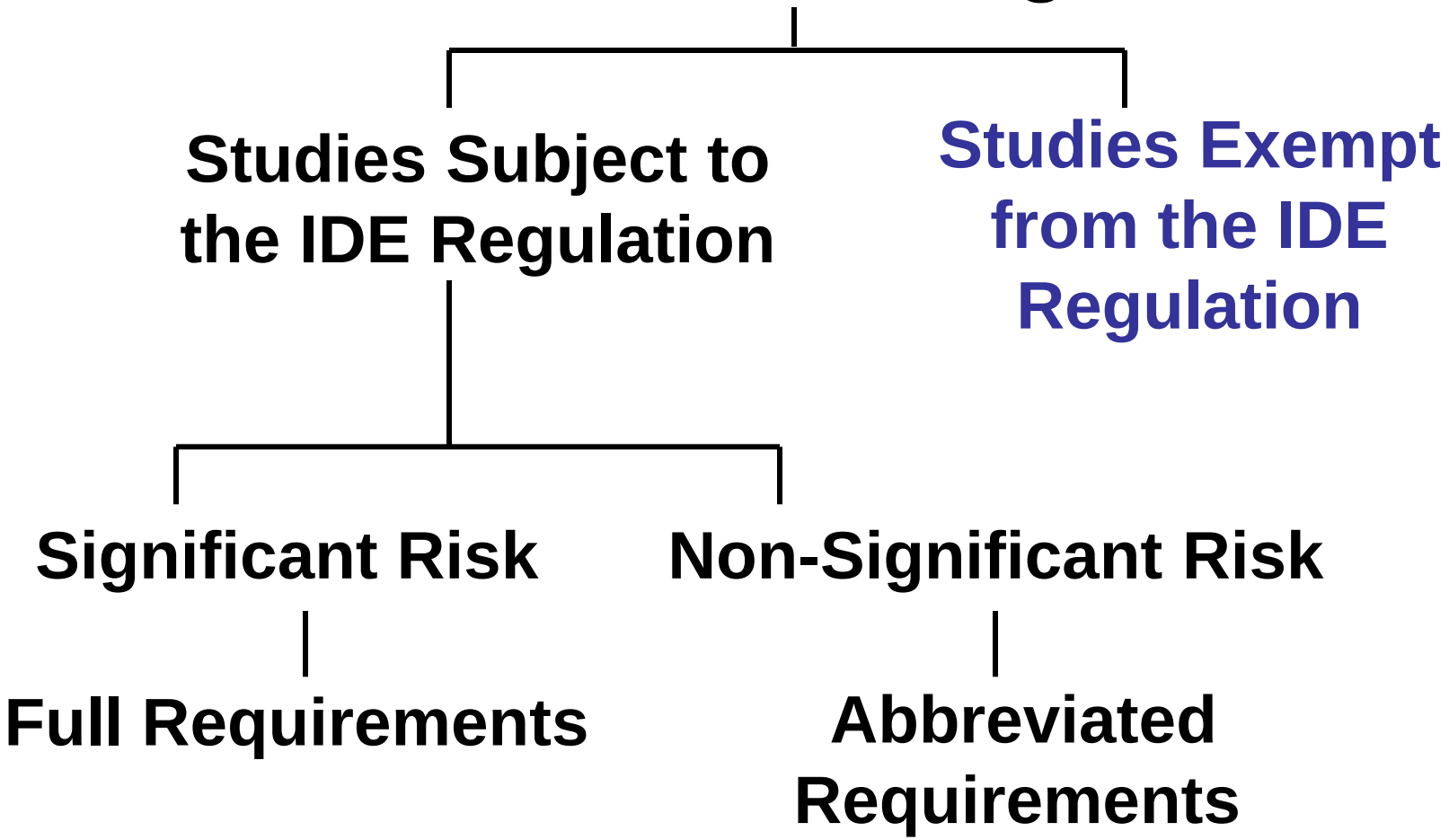
What if I have a high risk device?

- How do I develop my device?
- You may need an IDE…

Investigational Device Exemption (IDE):

- allows the investigational device to be used in a significant risk clinical study
- can be used to collect safety and effectiveness data to support a PMA or a 510(k) submission
  - most often conducted to support a PMA
- risk to patient balanced by anticipated benefits
- device labeled for investigational use only

All Device Investigations



IDE Exempt Investigations

Studies exempt from the IDE regulation include a diagnostic device that is:

- Non-invasive
- Does not require an invasive sampling procedure that present significant risk
- Does not by design or intention introduce energy into a subject
- Is not used as a diagnostic procedure without confirmation by another medically established diagnostic product or procedure

Studies exempted from IDEs still require:

- informed consent (if possible)
- IRB oversight (if needed),
- inspections,
- adherence to investigational protocols,
- pertinent reports and record-keeping,
- distribution controls

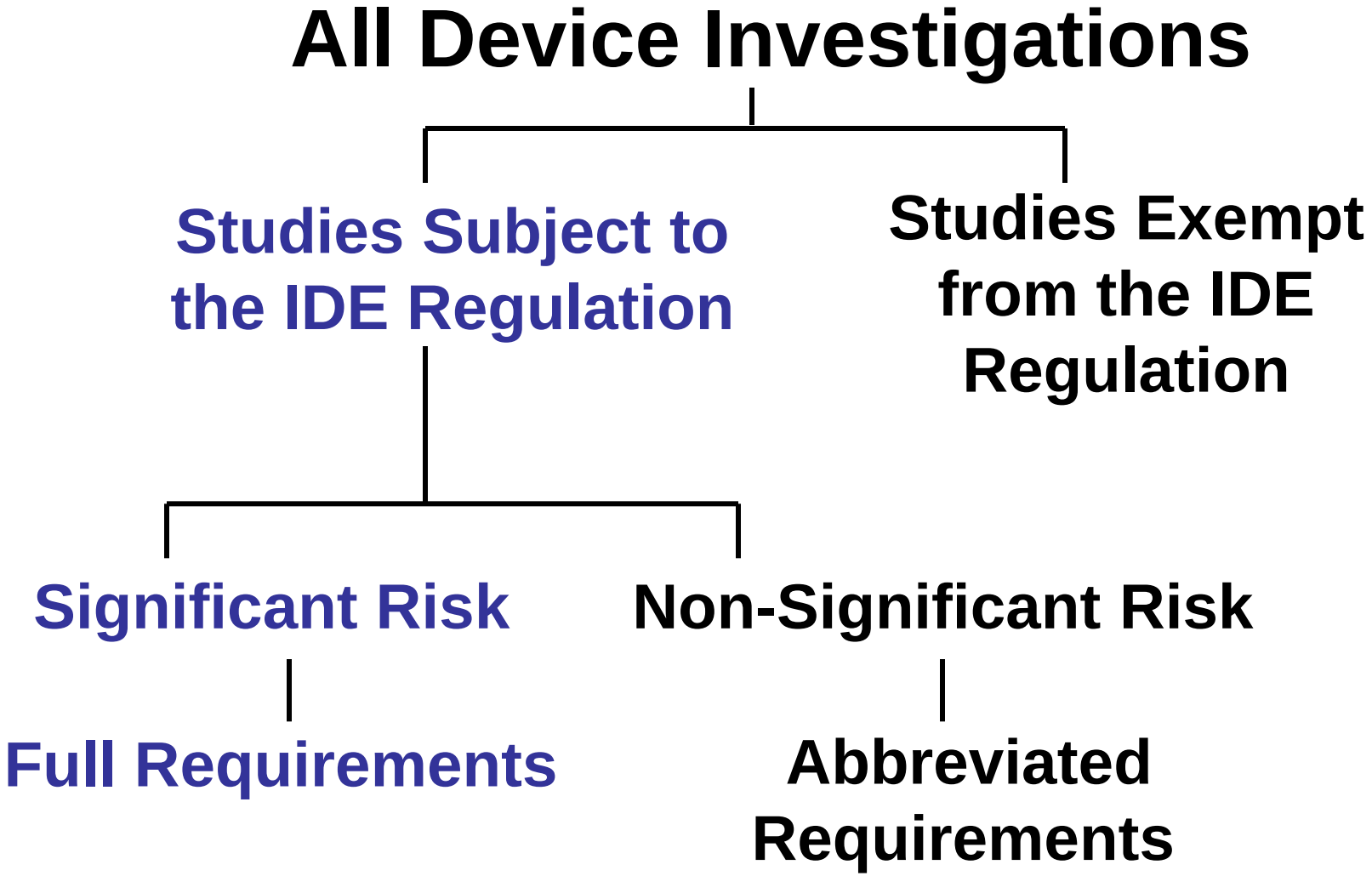
- Compliance with the FDA's regulations and scientific standards

All Device Investigations

- **Studies Subject to the IDE Regulation**
  - **Significant Risk**
    - **Full Requirements**
  - **Non-Significant Risk**
    - **Abbreviated Requirements**
- **Studies Exempt from the IDE Regulation**

*If not **Exempt** from Device Regulation, then…*

- Need to assess whether proposed study of device is considered **Significant Risk (SR),** or **Non-significant Risk (NSR)**
- IRBs can and do make this assessment most of the time
- If IRBs or sponsors need assistance in making or request that FDA make risk determinations, FDA's determination is final


All Device Investigations
Studies Subject to the IDE Regulation
Studies Exempt from the IDE Regulation
Significant Risk
Non-Significant Risk
Full Requirements
Abbreviated Requirements

Significant Risk Study

Presents a **potential for serious risk** to the health, safety, and welfare of a subject and is:

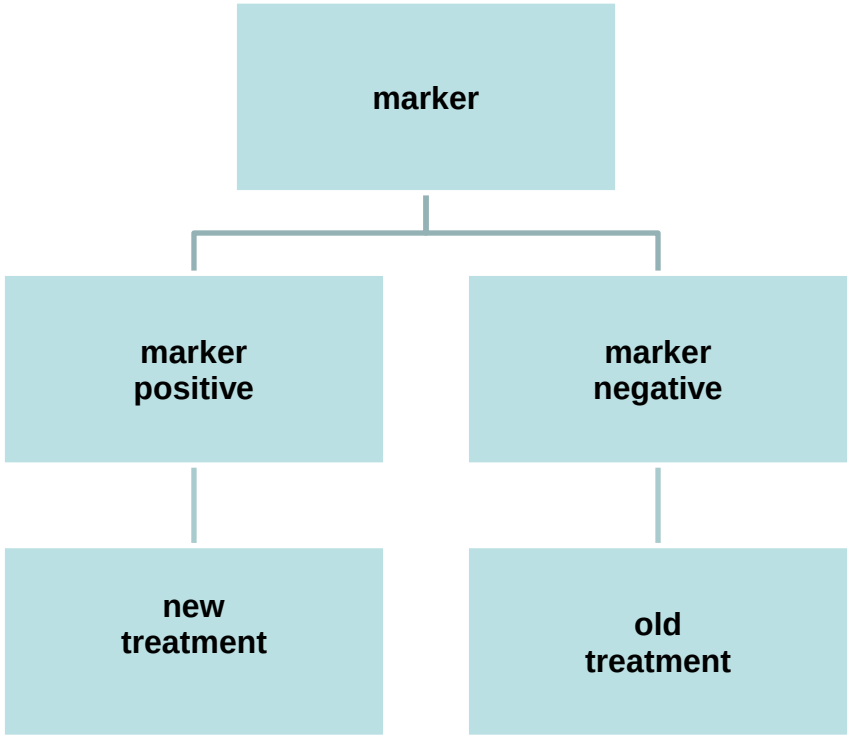
- an implant; or
- used in supporting or sustaining human life; or
- of substantial importance in diagnosing, curing, mitigating, or treating disease or preventing impairment of human health

Significant Risk Studies

- Sponsor submits IDE application to FDA
- FDA approves, approves with conditions, or disapproves IDE within 30 calendar days
- Sponsor obtains IRB approval
- After both FDA and IRB approve the investigation, study may begin

Example of Significant Risk Study

- Marker used to select treatment



All Device Investigations

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- **Studies Exempt from the IDE Regulation**

Non-Significant Risk Studies

- Sponsor presents protocol to IRB and a statement why investigation does not pose significant risk
- If IRB approves the investigation as NSR, it may begin
- **Abbreviated** IDE requirements (labeling, IRB, informed consent, monitoring, reporting, prohibition of promotional activities)
- **No IDE** submission to FDA needed

HDE

Humanitarian Device Exemption

- Purpose: approval to market a class III (high risk) device for an unmet need in a patient population <4,000/year in the US
  - Must first obtain designation as a Humanitarian Use Device (HUD) from OOPD
- No MDUFA goals or fees
- Statutory timeframe: 75 days

- And HDE is similar in both form and content to a premarket approval (PMA) application, but is exempt from the effectiveness requirements of a PMA.
- HUD provision of the regulation provides an incentive for the development of devices for use in the treatment or diagnosis of disease affecting these populations.

Regulatory Classes: I, II, and III

- Three regulatory Classes – based on the level of control necessary to provide reasonable assurance of safety and effectiveness:
  - Class I – General Controls
  - **Class II – General Controls & Special Controls**
  - Class III – General Controls and Premarket Approval

Description of Classes I, II, and III

- General Controls include:
  - Prohibition against adulterated or misbranded devices
  - Premarket notification (510(k)) requirements
  - Banned devices
  - Good Manufacturing Practices
  - Registration of manufacturing facilities
  - Listing of device types
  - Record keeping
  - Repair, replacement, refund

Description of Classes I, II, and III

- Class II:

  1. Devices which cannot be classified into Class I because general controls by themselves are insufficient to provide reasonable assurance of the safety and effectiveness of such devices, but...
  2. For which there is sufficient information to establish special controls to provide such assurance.

Description of Classes I, II, and III

- Special Controls include:
  - Guidance
  - Performance standards
    - Discretionary, voluntary national or international standard, recognized by rulemaking
  - Postmarket surveillance
  - Patient registries

Description of Classes I, II and III

- Class III:

  1. Devices for which insufficient information exists to determine that general and special controls are sufficient to provide reasonable assurance of the safety and effectiveness of such devices; and
  2. Such devices:
     - Are life-sustaining or life-supporting;
     - Are of substantial importance in preventing impairment of human health; or
     - Present unreasonable risk of illness or injury

Classification of Post-Amendment Devices

- The 510(k) process is used to classify individual post-amendment devices:
  - Either find a device substantially equivalent to a predicate; or
  - Find a new device that must be placed automatically into class III and require PMA, de novo, or reclassification before marketing in U.S

So 510(k) is…

- Premarket Notification
- Section 510(k) of FFD&C Act
- 21 CFR 807 Subpart E
- Determination regarding marketing clearance
- A process that allows FDA to make a determination regarding Substantial Equivalence (SE)
- The classification process for an individual device
- 1986 Guidance on the CDRH Premarket Notification Review Program
  - http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm081383.htm

A 510(k) is required when…

- Introducing device to the market for the first time
- Changing a device's indications for use
- Making significant modification to device that could affect safety or effectiveness

A Device is SE if…

- In comparison to a predicate device it:
  - Has the same intended use, and
  - Has different technological characteristics and the information in the 510(k):
    - Does not raise different questions of safety and effectiveness, and
    - Information submitted demonstrates, including appropriate clinical or scientific data, it is at least as safe and effective as the predicate
- Approximately 85% have been determined to be SE

A Device is NSE if…

- There is no predicate device; or
- It has a new intended use; or
- It has different technological characteristics compared to the predicate device and it raises a different type question of safety and effectiveness; or
- It does not demonstrate that it is at least as safe and effective as the predicate.

Not Substantially Equivalent

- Approximately 3% – 4% have been determined NSE (remaining ~10% are withdrawn or not-a-device).
- Data is looked at last in the 510(k) regulatory process.
- FDA usually asks for additional information at least once prior to determining the device is NSE for lack of data.

Regulatory Classes: I, II, and III

- Three regulatory Classes – based on the level of control necessary to provide reasonable assurance of safety and effectiveness:
  - Class I – General Controls
  - Class II – General Controls & Special Controls
  - **Class III – General Controls and Premarket Approval**

Traditional PMA

- Required elements can be found in 21 CFR 814 and section 515 of the Food Drug & Cosmetic Act

OIR PMA Decision Goals	
	FDA Days
Original PMA and Panel-Track Supplement without panel	**180**
Original PMA and Panel-Track Supplement with panel	**320**
Modular PMA*	**90**
Modular PMA Shell*	**14**
180-Day Fee Supplement	**180**
180-Day No-Fee Supplement*	**180**
Real-Time Supplement	**90**
Annual Report*	**90**
30-Day Notice	**30**
Special Changes Being Effected (CBE)*	**30**
*non-MDUFA III goal (internal goal only)	

Additional PMA Guidances

- Modifications to Devices Subject to Premarket Approval (PMA) – The PMA Supplement Decision-Making Process (Dec 11, 2008) http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm089274.htm
- Types of Communication During the Review of Medical Device Submissions (March 5, 2013) - http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm341918.htm
- PMAs: Effect on FDA Review Clock and Goals (October 15, 2012) - http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm089733.htm
- eCopy Program for Medical Device Submissions (December 31, 2012) - (http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM313794.pdf
- Bundling Multiple Devices or Multiple Indications in a Single Submission (June 27, 2007) - http://www.fda.gov/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm089731.htm

Office of Combination Products

- a product composed of any combination of a drug and a device; a biological product and a device; a drug and a biological product; or a drug, device, and a biological product. Under 21 CFR 3.2 (e), a combination product is defined to include:

1. A product comprised of two or more regulated components (i.e., drug/device, biologic/device, drug/biologic, or drug/device/biologic) that are physically, chemically, or otherwise combined or mixed and produced as a single entity (Monoclonal antibody combined with a therapeutic drug).

2. Two or more separate products packaged together in a single package or as a unit and comprised of drug and device products, device and biological products, or biological and drug products (Drug or biological product packaged with a delivery device)

3. A drug, device, or biological product packaged separately that according to its investigational plan or proposed labeling is intended for use only with an approved individually specified drug, device, or biological product where both are required to achieve the intended use, indication, or effect and where, upon approval of the proposed product, the labeling of the approved product would need to be changed (e.g., to reflect a change in intended use, dosage form, strength, route of administration, or significant change in dose) (Photosensitizing drug and activating laser/light source)

4. Any investigational drug, device, or biological product packaged separately that according to its proposed labeling is for use only with another individually specified investigational drug, device, or biological product where both are required to achieve the intended use, indication, or effect.

Office of Combination Products

- Recent examples of combination product approvals may be found on the OCP website.
- The roles of the Office of Combination Products (OCP) are:
  - To serve as a focal point for combination product issues for agency reviewers and industry
  - To develop guidance and regulations to clarify the regulation of combination products
  - To assign an FDA center to have primary jurisdiction for review of both combination and single entity (i.e., non-combination) products where the jurisdiction is unclear or in dispute.

http://www.fda.gov/CombinationProducts/AboutCombinationProducts/ucm118332.htm

Companion Diagnostics

- An *in vitro companion diagnostic device* is an in vitro diagnostic device that provides information that is essential for the safe and effective use of a corresponding therapeutic product. The use of an IVD companion diagnostic device with a particular therapeutic product is stipulated in the instructions for use in the labeling of both the diagnostic device and the corresponding therapeutic product, as well as in the labeling of any generic equivalents and biosimilar equivalents of the therapeutic product.

Companion Diagnostics

- http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/ucm301431.htm

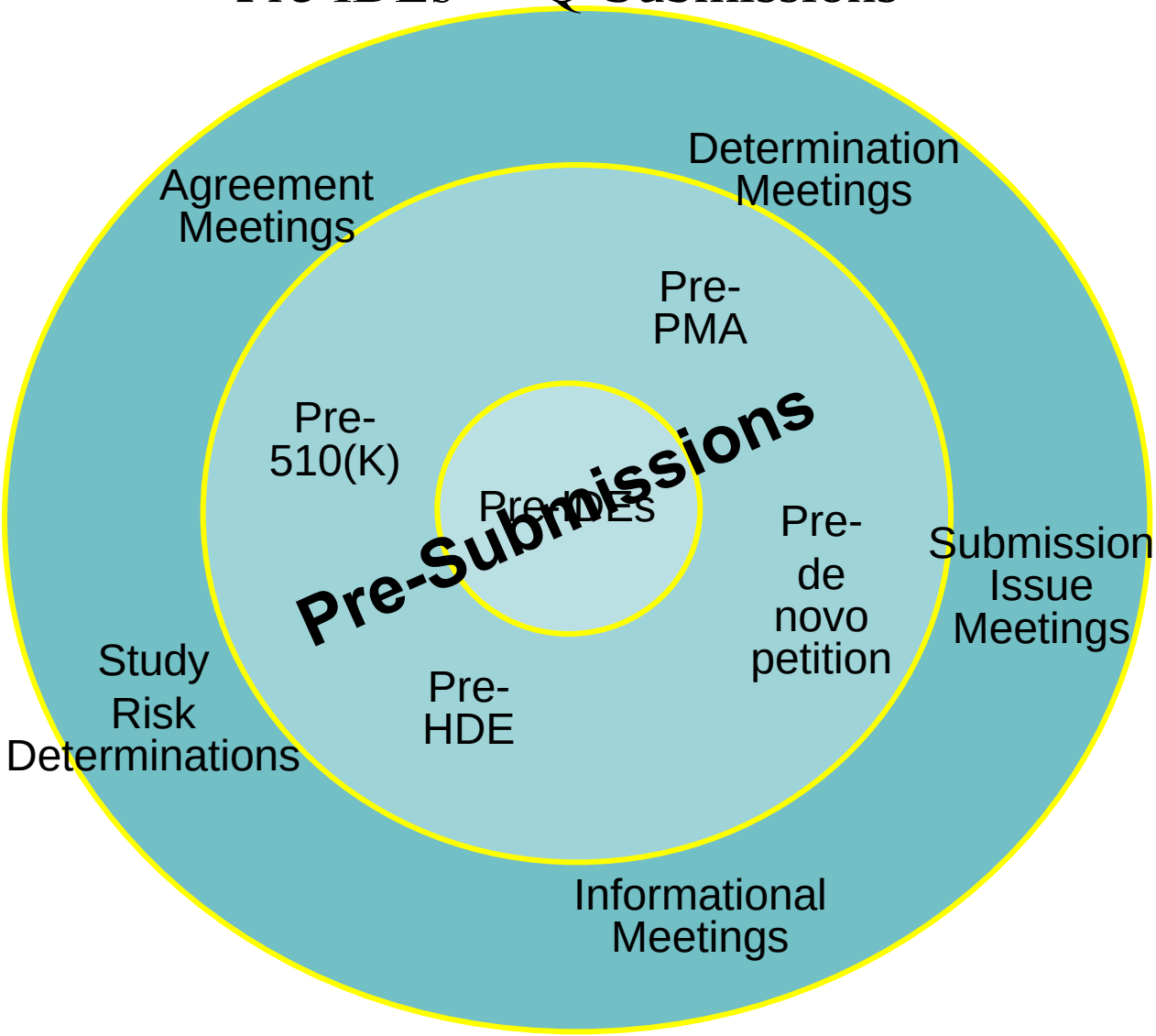
- The *therascreen* KRAS RGQ PCR Kit is a real-time qualitative PCR assay used on the Rotor-Gene Q MDx instrument for the detection of seven somatic mutations in the human KRAS oncogene, using DNA extracted from formalin fixed paraffin-embedded (FFPE) colorectal cancer (CRC) tissue. The *therascreen* KRAS RGQ PCR Kit is intended to aid in the identification of CRC patients for treatment with Erbitux (cetuximab) based on a KRAS no mutation detected test result.

- HER2 FISH PharmDx kit is a direct fluorescence in situ hybridization (FISH) assay designed to quantitatively determine HER2 gene amplification in formalin-fixed, paraffin-embedded (FFPE) breast cancer tissue specimens and FFPE specimens from patients with metastatic gastric or gastroesophageal junction adenocarcinoma.

  HER2 FISH PharmDx Kit is indicated as an aid in the assessment of patients for whom Herceptin (trastuzumab) treatment is being considered and for breast cancer patients for whom Perjeta (pertuzumab) treatment is being considered (see Herceptin and Perjeta package inserts).

  For breast cancer patients, results from the HER2 FISH pharmDx Kit are intended for use as an adjunct to the clinicopathologic information currently used for estimating prognosis in stage II, node-positive breast cancer patients.

Pre-IDEs → Q-Submissions



Q-Submissions

Q-Submission Type	Meeting	Timeframe for Meeting/Teleconference (from receipt of submission)
Pre-Submission*	Upon request	75-90 days**
Informational Meeting	Yes	90 days
Study Risk Determination	No	N/A
Agreement Meeting	Yes	30 days or within time frame agreed to with sponsor
Determination Meeting	Yes	Scheduled within 30 days of request
Submission Issue Meeting	Yes	21 days
PMA Day 100 Meeting	Yes	100 days (from filing of PMA)

The Pre-Submission Program

Considered a key part of MDUFA III

- Beneficial for FDA and Industry
  - Industry desire to understand FDA's expectations *before* submission
    - Design testing and development plans that will facilitate FDA review – get FDA "buy in" early
    - Improve submission quality, if FDA feedback is addressed
  - Build relationships and understanding
  - Educate the review team on novel technology
  - Minimize "surprises" during the review process

Definition of a Pre-Submission*

- A formal written request from an applicant for feedback from FDA
  - provided in the form of a formal written response or a meeting or teleconference in which the feedback is documented in meeting minutes
- When FDA's feedback on specific questions is necessary to guide product development and/or application preparation (i.e., prior to intended submission of an IDE or marketing application)
- Request must include specific questions regarding review issues relevant to a planned IDE or marketing application (e.g., questions regarding pre-clinical and clinical testing protocols or data requirements).

*From the MDUFA III Commitment Letter

A Pre-Sub is:

- Intended to be specific to the questions posed
  - however, if other deficiencies or concerns are noted during review, they may be included in FDA's feedback.
- Generally meant to be a one-time process per topic (i.e., not iterative)
  - but can be utilized at different times and/or for multiple topics for the same device (e.g., prior to IDE submission for bench testing and clinical protocols, then prior to PMA submission regarding data presentation).
  - If significant changes are made to sponsor's proposal in response to initial FDA feedback, may be appropriate to engage in repeat interaction on the same topic.

A Pre-Sub is NOT:

- A mechanism for FDA to design nonclinical test or clinical study protocols for the sponsor
- Phone calls or emails regarding questions that can readily be answered by the reviewer (+/- routine involvement of the supervisor or mentor)
- Interactive review of an active submission
- An RFD, 513(g), or appeal

When to submit a Pre-Sub?

General Considerations

- Voluntary, but encouraged
- Prior to initiating long term preclinical studies
- When planning a study that does not require an IDE
  - Studies that are outside the US, exempt, or NSR
- Before submission of an IDE to:
  - Discuss nonclinical data and clinical study design
- Before submission of a marketing application to:
  - Apprise FDA review team on specifics of device and clinical study if there have been changes since initiation of the IDE
  - Obtain feedback on preferred data presentation
  - Gain insight into potential hurdles for approval of clearance
- When preparing a submission for a new device that does not clearly fall within an established regulatory pathway

When to submit a Pre-Sub?

IVD-Specific Considerations

- Before conducting clinical, nonclinical, or analytical studies or submitting a marketing application for a new IVD that:
  - Is a multiplex device capable of simultaneously testing a large number of analytes
  - Contains a new technology
  - Has a new intended use
  - Includes a new analyte
  - Presents new clinical questions
  - Presents complex data/statistical questions
  - Uses a predicate or reference method that is unclear or uncertain

Pre-Sub Process: Step 1

Sponsor submits to DCC

- DCC Address
  - Include E-copy
- Cover letter should include:
  - Identification as a "Pre-Submission"
  - Sponsor contact information
  - Device name
- Contents
  - Device description
  - Proposed indications for use
  - Summary of previous discussions/submissions re same device
  - Overview of planned product development
  - Specific questions for FDA feedback
  - Desired mechanism for feedback (i.e., written, meeting, tcon)

U.S. Food and Drug Administration
Center for Devices and
Radiological Health
Document Control Center –
WO66-G609
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

FDA Feedback on a Pre-Sub

- Feedback represents FDA's best advice based on the information provided
- FDA intends to stand behind our feedback unless:
  - Information in subsequent submission is not consistent with Pre-Sub (e.g., change in proposed indication for use or device design)
  - Data in the subsequent submission raise important new issues related to safety and effectiveness (e.g., a study is conducted as recommended by FDA, but results raise new safety concerns)
  - Feedback given previously does not adequately address important new issues materially relevant to a determination of safety or effectiveness that have emerged since the time of the Pre-Sub (e.g., new alternative therapies/diagnostics have emerged since discussion of the clinical protocol making the previously recommended study design unethical)

Other Mechanisms for FDA Feedback

Mechanisms for FDA Feedback

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Informational Meeting	Yes	90 days
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Determination Meeting	Yes	Scheduled within 30 days of request
Submission Issue Meeting	Yes	21 days
PMA Day 100 Meeting	Yes	100 days (from filing of PMA)

Informational Meetings

- Purpose: to share information with FDA
- May be appropriate to:
- Provide an overview of ongoing device development when there are multiple submissions planned within the next 6-12 months, or
- Familiarize the review team about new device(s) with significant differences in technology from currently available devices.
- NO expectation of feedback, although review team may ask questions or offer suggestions if appropriate
- Granted as resources allow
- If granted, should be scheduled within 90 days
- Meeting package should contain sufficient background information to allow FDA to identify appropriate attendees
- Follow meeting minutes procedure for Pre-Subs (although minutes may be much briefer)

Mechanisms for FDA Feedback

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Agreement Meeting	Yes	30 days or within time frame agreed to with sponsor
Determination Meeting	Yes	Scheduled within 30 days of request
Submission Issue Meeting	Yes	21 days
PMA Day 100 Meeting	Yes	100 days (from filing of PMA)

Study Risk Determinations

- Information Sheet Guidance for IRBs, Clinical Investigators, and Sponsors: Significant Risk And Non Significant Risk Medical Device Studies

http://www.fda.gov/downloads/regulatoryinformation/guidances/ucm126418.pdf

Tips for Successful Meetings with FDA

Available Guidance

The Pre-Submission Program and Meetings with FDA Staff

- Available in draft at: http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm310375.htm

•Final version will include:

– All types of feedback requests
– Information on tracking with "Q" numbers (ex. Q130001)
– Acceptance review process and checklists
– Edits to address comments received in public comment period

Early Collaboration Meetings Under the FDA Modernization Act (FDAMA)

•Available in final at: http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm073611.pdf

Best Practices for Meetings with FDA

- Follow the suggested logistics in the guidance document
  - Provide several options for dates to remain flexible
- Think carefully about what you want to get out of a meeting with FDA, then:
  - Submit focused questions in advance
  - Develop the agenda based on these questions
  - Bring the right experts to execute your objectives
- Do not expect FDA to:
  - Make guarantees or binding commitments
  - Hold to informal feedback provided years ago
  - Approve a study or clear/approve a device at the meeting
  - Act as a consultant
  - Have iterative meetings on the same topic – make the most of each meeting

Best Practices for Meetings with FDA

- FDA will prepare to ensure that the meeting is productive, make sure you are prepared as well
  - Do not send new questions/discussion topics at the last minute or during the meeting; FDA needs time to prepare
- Suggest limiting presentation of the information in the pre-meeting materials to 1/3 of the allotted time to allow for discussion
- Bring a dedicated attendee to take detailed notes
- Summarize action items at the close of the meeting and ask for clarification if needed
- Submit draft minutes on time, while the discussion is still fresh in minds
- Address FDA's feedback in your future submission

DSMICA: Division of Small Manufacturers, International and Consumer Assistance

- A division in CDRH's Office of Communication and Education
- Answer inquiries from industry and consumer stakeholders
- Address all aspects of medical devices and radiation programs
- Develop educational training for our stakeholders [workshops, video modules, written guidance]
- Manage small business determination (SBD)
- Industry assistance, premarket
- Industry assistance, postmarket

Small Business Determinations (SBDs)

- grant designation as a "small business"
- "small business" = gross receipts or sales ≤ **100M**
- annual guidance "FY 2013 Medical Device User Fee Small Business Qualification and Certification"
- granted status eligible through end of current fiscal year only
- must request each fiscal year no carry-over between years
- FDA reviews SB request within 60 days

Small Business Determinations (SBDs)

- **Benefit of SB Designation**
  - reduction of user fee costs for various applications
    - 510(k): **$2480** (standard fee - $4960)
    - 513(g): **$1674** ($3348)
    - PMA: **$62,000** ($248,000)
  - no reduction for registration and listing

- **# of requests in FY 2012: 1459**
  - ↑ trending upward (reflection of innovation, small business development)

- **DSMICA Email: industry.devices@fda.hhs.gov**

FDA Resources

Pre-Submission Program

http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm310375.htm

Device Advice

http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/default.htm

Medical Devices

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

-Guidance Documents,
-PMA Approvals with Labeling and Summary of Safety and Effectiveness
-510(k) Clearances with Summaries and Decision Summaries

Center for Devices and Radiological Health
CDRH

Thank you!

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Slides: Elizabeth Stafford; Elizabeth Hillebrenner; Marjorie Shulman; Kelly Wilkicki; Elias Mallis

- What does FDA look at during review?
  - Analytical
  - Clinical
  - Labeling

IUO vs. RUO

- **IUO: Investigational Use Only**
  - Product testing prior to full commercial marketing
  - Must be labeled “For Investigational Use Only. ”
  - Made under QSR design controls

- **RUO: Research Use Only**
  - Laboratory research phase of development,
  - Must be labeled “For Research Use only. Not for use in diagnostic procedures.”
  - Don’t have to be made under QSR

- Any IVD for non-investigational purposes, such as in clinical diagnostic use outside of an investigation, should **not** be labeled IUO.

Clinical Laboratory Improvement Act (CLIA 88)

- Clinical laboratory = any facility that tests samples to provide information to diagnose, prevent, and treat disease, or assess health
- Accuracy, reliability, timeliness of results
- CLIA's responsibility is to ensure proper performance of the test
  - specifies minimum standards for laboratories – personnel, QC and PT testing requirements

For tests approved/cleared by FDA…

- …CLIA requires verification of manufacture's stated performance
  - Limited testing
  - Document that the method performs as expected
- FDA categorizes commercially marketed IVDs on basis of technological complexity
  - Waived, moderate, high

For tests not approved/cleared by FDA…

- …or those modified by lab, CLIA requires validation and verification of performance specifications including:
  - Establish accuracy, precision, analytical sensitivity, specificity, reportable ranges
  - Continue to verify performance

	FDA	CLIA
Regulates	Drugs, Biologics, Devices, etc.	Laboratories - Operation and facilities - Requirements based on complexity of assays - Personnel (education/ training)
Research Phase	Yes	Not always
Performance requirement	Demonstrate safe & effective	None
Analytical validation	Yes, prescribed, standards	Ad hoc
Clinical validation	Yes	Typically limited

Manufacturing	Quality System Requirement
	- Designed & manufactured – controlled/consistent manner
	- Premarket/Postmarket controls
	  - Corrective/Preventive Action
	  - Recalls
		Limited

Report Adverse Events	Yes	Not normally
Transparent Results	Decision summaries/SSEDs publically available	No information on assay or laboratory performance

Lab Developed Test (LDT)

- Performed in a single, central, CLIA-certified lab
- Considered high complexity
- Evaluated and validated in developing laboratory
- Laboratory must determine suitability for clinical use
- Under FDA purview, i.e., *not* exempt from FDA regulation
- FDA has exercised “enforcement discretion” to date
- Concern about varying quality in test development and validation