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FDA Procedures – Clinical Trials and Marketing Approval in the US

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Outline

- Brief introduction to NAMSA
- Overview of US FDA medical device regulations [focusing on 510(k) submissions]
- Review of US Good Clinical Practices (GCP)

Introduction to NAMSA

NAMSA

Beyond Contract Research, NAMSA is a Medical Research Organization with more than 600 Associates dedicated to translating great ideas into marketed medical products.

- Medical Devices
- Combination Products
- *In vitro* diagnostics (IVDs)

NAMSA's MRO™ Approach to Testing and Consulting Services

NAMSA plays a key role in translating great ideas into marketed medical products, bringing a unique combination of services:

- Regulatory
- Quality
- Preclinical/Nonclinical
- Clinical

to move client products "from concept to bedside" more rapidly…

from the laboratory through clinical trials to actual point-of-care patient applications

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NAMSA Locations

Northwood, OH
Headquarters
Laboratory

Irvine, CA
Laboratory

Lyon, France
Laboratory

Brooklyn Park, MN
Laboratory

Minneapolis, MN
Clinical & Consulting

Sunnyvale, CA
Clinical & Consulting

Frankfurt, Germany
Clinical & Consulting

Shanghai, China
Clinical & Consulting

Translating Great Ideas

- Global regulatory assessment
- Design Controls
- Pre-Submission meetings
- Global Regulatory Strategy

- Preclinical Research & Model Development
- Test Method Development & Validation
- Quality Systems/ Quality Management
- Biocompatibility
- Training Seminars
- Materials Characterization

- Study Design & Management
- Biostatistics
- Data Management
- Report writing
- DSMB/CEC
- Physician Training
- IDE Submissions

- Global Marketing Applications
- FDA BIMO Inspections
- FDA Panel Meetings
- Packaging Validations

- Post-Market Clinical Trials & Registries
- Microbiology Testing
- Sterilization Assurance
- FDA Reporting Requirements

Overview of FDA Medical Device Regulations

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Multiple Requirements for US Market Entry

- Quality System Regulations (QSR)
- Investigational Device Exemption (IDE) [for most clinical studies]
- Premarket Notification 510(k) or Premarket Approval (PMA)
- Labeling requirements
- Establishment Registration
- Medical Device Listing
- Medical Device Reporting (MDR)

Quality System Regulations (QSR)

- Defined by Title 21, Code of Federal Regulations, Part 820 (21 CFR 820) - Similar to ISO 13485
- FDA provides several useful guidance documents, e.g. *Guide to Inspections of Quality Systems*
- FDA inspection starts with Management Controls, Design Control, Corrective & Preventive Action, Production & Process Controls
- If initial inspection identifies problems, FDA will dig into other elements of the QS and follow the path of documentation
- FDA issues Form FDA 483 for observed deficiencies. For gross deficiencies, FDA issues a Warning Letter (published on web)
- Design control processes must be used during development

Quality System Regulations (QSR)

- Relative to Notified Bodies (NBs), FDA has a stronger concern about the link between the QS and product safety and effectiveness
- FDA is especially concerned about the processing of Complaints and Non-Conforming Product reports - and follow-through corrective/preventive actions
- FDA will pursue an investigation from top level documents to specific records such as training records, device history files (manufacturing lot records), non-conforming product reports (and associated investigations) to evaluate whether the company is taking specific action to respond to product problems
- In contrast, Notified Bodies focus more on the documented compliance with the processes set out by ISO 13485, being more concerned about the QS process than the immediate implications about product performance
- NB auditors are more likely to review a larger percentage of higher level documents than FDA, while spending less time on lower level quality records

Three Classes of Medical Devices

- In general:
  - Class I – Exempt from 510(k) submission
  - Class II – 510(k) submission
  - Class III – Premarket Approval (PMA)
- Class I Exemption has limitations. For example, new technology can trigger a 510(k).
- Some Class II devices are exempt from 510(k)
- Some Class III devices require only a 510(k)
- ≈ 80% of new medical devices require 510(k) submissions

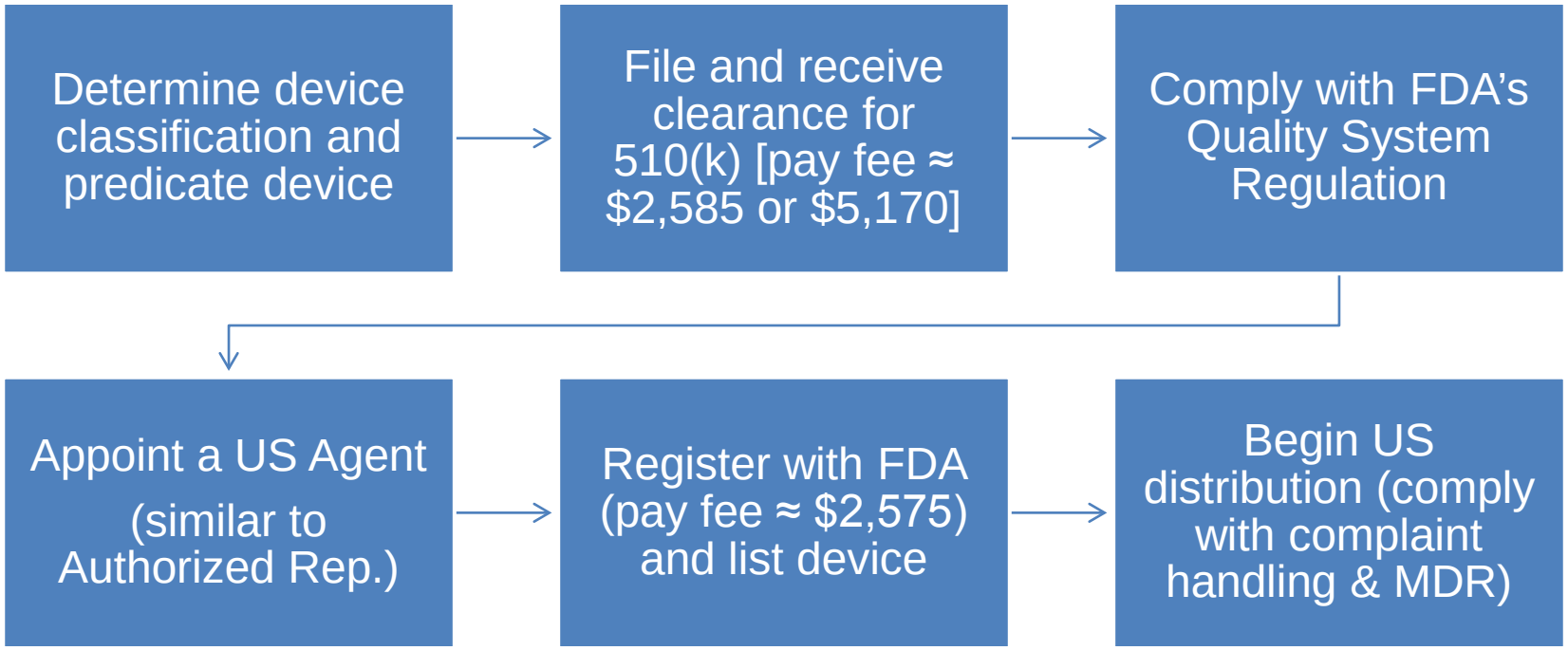
510(k)s vs. PMA

- 510(k)s
  - Clinicals less common
  - Submission is shorter
  - FDA *marketing clearance* takes 3 – 6 months
  - Minor modifications to the product after FDA clearance do not require a new 510(k)
  - Many modifications require only a Special 510(k) – short submission with FDA clearance in 1 - 2 months
  - Changes in intended use or fundamental technology require a new 510(k)

510(k) vs. PMA

- PMAs
  - Animal trials common and (large) clinicals usually required
  - Submission is long, detailed, and describes manufacturing processes. Review fees of ≈ $260,000 [large companies]; fee waived for small companies for 1st PMA, reduced to ≈ $64,000 for subsequent PMAs.
  - FDA *approval* takes 1 – 2 years, with pre-approval QS inspection
  - FDA pre-approves most modifications with costs of ≈ $4,500 to $193,000 depending on the change and size of the company
  - Changes in intended use or significant changes in technology require a new PMA

Steps to Marketing Class II Product in the US (non-US Manufacturer)



510(k) Process

- Standard for “marketing clearance” is “substantial equivalence” to a Class II device legally marketed in the US, a “predicate device”
- In contrast with the EU classification system, the US system is still tied to medical device history and is not ruled only by a well-defined, risk-based classification system
- Starting point: FDA’s Classification Database to identify the classification and potential predicates: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPCD/PCDSimpleSearch.cfm

Substantial Equivalence

For a device to be “substantially equivalent” to a legally marketed predicate device it must:

- Have the same intended use and the same technological characteristics of the predicate device, or…
- Have the same intended use and different technological characteristics, but:
  - does not raise new questions of safety and effectiveness, and
  - the data submitted to FDA demonstrate that the device is at least as safe and effective as the legally marketed device.

Predicate Devices

- It is key to be strategic when selecting a predicate device
  - Recommended to get expert opinion when choosing.
- Intended Use
  - In order to succeed with a 510(k) your device must have the same Intended Use as the predicate device
    - Intended use is the general use of the device
    - Indications for use is the specific use of the device
    - While a predicate may have a different indications for use statement and still share the same intended use, submission risk is reduced when the predicate device indication for use statement is identical to the subject device.

Predicate Devices

- Sometimes companies label their devices with a different indication for use than they would like:
  - Quicker path to market due to existing predicate
  - Allows firm to gain initial experience with device in the market
  - But may limit how the company may market the device
- FDA is concerned about off-label usage:
  - May require a limitation (e.g. “not for dura mater replacement”)
  - May disallow product (e.g. rejecting very limited claims for an IVD for Alzheimer’s disease due to risks of off-label usage)
  - May require proof of clinical usefulness, not just showing that the product “does what it claims to do”

Predicate Devices - Selection

- Select primary predicate, with secondary predicates to support specific features not covered by primary
- FDA does not allow split predicates (one predicate with same intended use and another device with same technological characteristics)

Predicate Devices – Practical Considerations

- If possible and practical, choose newer predicate devices
- Avoid predicates that have current safety-related issues
- Choose devices to which your device compares favorably, but beware choosing a device that has been shown to be inferior to another cleared device
- There is no statutory requirement for medical devices to represent “state of the art”, but FDA is hesitant to clear a device that is not as safe and effective as other, recently cleared, options

510(k) Application Contents

- Section 1: User fee cover sheet
- Section 2: CDRH Submission Cover Sheet
- Section 3: 510(k) Cover Letter
- Section 4: Clinical Trials.gov Form
- Section 5: Indications for Use
- Section 6: 510(k) Summary
- Section 7: Truthful and Accurate Statement
- Section 8: Class III Summary and Certification (if applicable)

510(k) Application Contents

- Section 9: Financial Certification of Disclosure Statement
- Section 10: Declaration of Conformity and Summary Reports
- Section 11: Executive Summary
- Section 12: Device Description
- Section 13: Substantial Equivalence
- Section 14: Proposed Labeling
- Section 15: Sterilization and Shelf Life

510(k) Application Contents

- Section 16: Biocompatibility
- Section 17: Software
- Section 18: EMC and Electrical Safety
- Section 19: Performance Data – Bench
- Section 20: Performance Data – Animal
- Section 21: Performance Data – Clinical
- Section 22: Other

510(k) Preparation

- FDA user fees 2013 – $4,960 ($2,480 small business)
- Be sure to address any relevant FDA guidances (device-specific, biocompatibility, etc.)
- 510(k)s should tell the device's "story"
  - A 510(k) is not just a "dossier", but should be written to convince FDA that the product is substantially equivalent to the predicate (and safe and effective)
  - FDA reviewers have time constraints dictated by the US Congress. The body of the 510(k) should summarize the information, make arguments for "substantial equivalence", and anticipate FDA questions – and then immediately put them to rest. Make it easy for the FDA reviewer.

510(k) Preparation

- Outline the argument that you are making
  - A 510(k) is not showing conformance to a product specification, but is making a comparison to a predicate device (although conforming to relevant standards is important).
  - Explain how the product has the same intended use and “technological characteristics” as the predicate
    - If it doesn’t, then clearly lay out your argument for how your device is at least as safe and effective as the predicate

FDA 510(k) Review Process

- FDA can refuse to file (review) the 501(k) if it is incomplete - submit complete, well-organized submissions
- FDA will almost always ask for “additional information”)
  - If the request is unclear, ask FDA for clarification
  - Respond fully – After the initial 510(k) review, FDA allows only two more rounds of review. If your response to the third and last review is not good enough, FDA will find the 510(k) “Not Substantially Equivalent” and you must submit a new 510(k), pay the user fee again, and wait another 2 - 3 months before FDA reviews the submission again.

Good Clinical Practices in the US

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Types of Device Clinical Trials

- Investigational Device Exemption (IDE) Study
  - Unapproved product and/or indication for use
  - Significant risk to patients (e.g. implant)
  - FDA *and* IRB approval needed
- Non-Significant Risk (NSR) Study
  - Unapproved product and/or indication for use
  - Non-significant risk to patient (e.g. intravenous blood sampling)
  - IRB approval only needed

Where / How to Conduct Clinical Studies

- FDA often accepts studies conducted out of the US
- FDA must agree that:
  - The study design and conduct meets FDA requirements
  - The results will reflect clinical results that can be expected in the US with US physicians, healthcare delivery system, and patients
  - For example, FDA would not allow testing a prostate cancer in vitro diagnostic (IVD) device with prostate samples collected in Europe, because doctors do not collect samples at the same stage of cancer or in the same number in Europe as is the standard of care in the US
- FDA clinical study requirements are rigorous; get FDA feedback on a protocols (including statistical analysis plan) before conducting studies with a “Pre-Submission” meeting

General Clinical Requirements

- Good Clinical Practice (GCP)s govern all clinical studies submitted to FDA
  - Provides assurance that a subjects health, confidentiality, and rights are protected
    - IRB oversight
    - Informed consent
  - Provides assurance that data and reported results are accurate
    - Clinical protocol and formal procedures (consistency of use and data collection requirements)
    - Data management (data capture and storage)
    - Monitoring to verify data collected
    - Statistical analyses and report generation

Protection of Research Subjects

- Provisions for Research Subject Protection
  - Requirements for Oversight Body (IRB/EC) 21 CFR Part 56
  - Requirements for Subject Informed Consent 21 CFM Part 50

Assurance of Valid Data

- Current Provisions for Assuring Valid Data
  - Sponsor Monitoring Requirements (21 CFR 812)
  - FDA Inspection Requirements—Bioresearch Monitoring Program (BIMO)
  - FDA Disqualification/Restriction/Debarment
    - For repeated or deliberate failure to comply with applicable regulatory requirements…or…
    - Repeated or deliberate submission of false information to the sponsor or, if applicable, to FDA

Key Responsibilities

- Sponsor - a person who initiates, but does not actually conduct, a clinical investigation
  - Monitor - an individual designated by a Sponsor or CRO to oversee the progress of an investigation
- Investigator - an individual who actually conducts a clinical investigation, i.e., under whose immediate direction the test article is used on a subject
- IRB (Institutional Review Board)/IEC (Independent Ethics Committee) - groups that review clinical studies to assure the protection of the rights and welfare of human subjects

Recordkeeping: Clinical Protocol

- Document that describes the objective(s), design, methodology, statistical considerations, and organization of a clinical trial
  - Optimize scientific validity of results
  - Evaluate safety and performance of the product
  - Specify study methods

Recordkeeping: Clinical Study Records

- Protocol History
- Ethics Committee Review Records
- Investigator Qualifications/Agreements
- Product Shipping/Accountability Records
- Monitoring Records
- Subject Consent and Study Records (Case Report Forms)
- Study Reports (summary of entire study)

Sponsor Responsibilities

- Select Investigators
  - Qualified/trained/familiar with disease and treatment
  - Agreed to meet study requirements including:
    - Compliance with laws
    - Intent to take every precaution to protect safety of subjects

Sponsor Responsibilities cont.

- Provide study information (investigator brochure)
  - Background literature
  - Device description with statement of intended performance
  - Previous clinical history
  - Bench and animal testing summaries
  - Investigational plan
- Train investigators and support staff
- Provide study product

Sponsor Responsibilities cont.

- Prepare, assemble and maintain preclinical data, clinical data and documentation
  - Investigation Plan
  - IEC/IRB opinions
  - Agreements
  - Case Report Forms (CRFs – for data collection)
  - Adverse Events
  - Final Report

Sponsor Responsibilities cont.

- Ensure NO improper inducements to investigators, monitors or staff
- Track/record Adverse Events (AEs)
  - Ongoing safety evaluation
  - Inform other investigators/IRBs about serious unexpected AEs in the study within 10 days
- Terminate the study, if necessary

Investigator Selection

Sponsor

- Key, practical qualifications:
  - Current technology users in the therapeutic area
  - Not be prohibited from performing research by the FDA (i.e., “blacklisted”)
  - Adequacy of equipment and facilities to conduct study
  - Willing and able (time commitment) to conduct the study
  - Willing to accept the responsibilities cited in the GCP regulations

Investigator Agreements

- Formal agreement that details the investigators commitment to participate
  - Description of trial and investigator (and co-investigator) responsibilities
  - Agreement to allow Sponsor access to investigation records
  - Confidentiality requirements
  - Publication arrangements/restrictions
  - Financial arrangements
- Task is very time consuming!

Investigator Training Procedures

Sponsor

- Protocol-Specific
  - Assessing patients
  - Enrolling patients
  - Following patients
- Device or Technology-Specific
  - Treating patients
  - Device use, disposal, tracking
- Reporting

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Investigator Training Protocol

- Careful patient selection (inclusion/exclusion)
- Obtain Consent Form
- Perform necessary baseline tests
- Use device appropriately
- Perform necessary follow-up tests
- Understand important protocol requirements and comply with them
- Record any deviations and reasons for deviations

Investigator Training-Device Use

Sponsor

- Selection of one consistent technique
  - Require uniform therapy among patients
  - Require uniform measurement/application technique
  - Control procedure-related variables
  - Ensure objective assessment of the device safety, efficacy & handling characteristics
  - Help identify, implement necessary refinements, adjustments, or chances

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Investigator Training-Data Collection

- Case Report Forms
- Patient Diaries
- Patient history notes, files, lab tests, CTs
- Specific investigation requirements for AEs, autopsies, etc.
- Verbal and written notes
- All other required documentation

Investigator Responsibilities

- Request and obtain necessary information from Sponsor
- Follow investigational plan
- Ensure adequate recruitment of subjects (based on retrospective data)
- Ensure availability of time and resources
- Train staff personnel and any co-investigators on investigational plan
- Ensure there is no conflict of interest (with other studies in which the investigator might be participating)

Investigator Responsibilities cont.

- Provide information to the Independent Ethics Committee (IEC) or Institutional Review Board (IRB)
  - Justification of scientific merit of the study
  - Assessment of how the patients health status might be affected (risks and methods of treatment)
  - Procedures to ensure patient confidentiality
  - Method of study supervision
  - Investigator qualifications
- Wait for approval from the IEC/IRB to initiate study

Investigator Responsibilities cont.

- Provide patients with study contact information, mark medical record to denote study participation and notify patients' primary physician
- Obtain necessary information from subjects
  - Ensure patient has disclosed all matters concerning health history and current medications
  - Understanding of payments (if applicable)-only covers time, expenses and inconvenience

Investigator Responsibilities cont.

- Obtain informed consent from patients
  - Consent topics
    - Aims, benefits and risks (and inconveniences) of study
    - Explanation of alternative treatments
    - Consequences of withdrawal (freedom to do so without sanctions)
    - Confidential but not anonymous
    - Address how emergencies will be handled
  - No language about “waiver of legal rights” or “release of entities from liability for negligence”
  - Allow adequate time to decide; witness to process if patient is unable to read

Investigator Responsibilities cont.

- Maintain product accountability (procedures)
- Discuss and obtain necessary approvals for protocol chances prior to implementation
- Maintain accurate, legible records in a secure manner
  - Sign and date all CRFs
  - Sign and date any alterations to data
  - Document any deviations or lack of informed consent
  - No subject's identity can be released without written consent

Investigator Responsibilities cont.

- Report Adverse Events to Sponsor and IRB
- Ensure established procedure for handling AEs
- Provide patients with any new safety information about the study
- Safeguard patients interest in any emergency
  - Such deviations do not require prior approval
  - Such deviations will not be considered breach of agreement
- Review and sign final report

Good Clinical Practice Resources

- Compilation of FDA Regulations
  - 21 CFR 50, 54, 56, 312, 812
- International Conference on Harmonization: Good Clinical Practice: Consolidated Guideline
  - ICH Harmonized Tripartite Guideline, 1996
    - Unified Standard for EU, Japan, USA
- FDA Guidance Documents and Information Sheets
- ISO 14155 Clinical investigation of medical devices (Complementary Standard)
- Directive 2001/20/EC, dated April, 2001 – became effective May, 2004

FDA Regulations Governing Clinical Research

21CFR 56	Institutional Review Boards (IRB)
21CFR 812	Investigational Device Exemption (IDE)
21CFR 814	Premarket Approval Application
21CFR 50	Protection of Human Subjects
21CFR 54	Financial Disclosure by Clinical Investigators

In total, these regulations constitute the concept of GCP

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