

Path to FDA Marketing Approval of Medical Devices

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FDA Device Regulation Overview

- Center for Devices and Radiological Health (CDRH)
- Pre and post market requirements 21 CFR 8xx
- Steps:
 - ▶ Confirm device meets the definition of a medical device with CDRH
 - ▶ Identify device as Class I, II or III (based on risk-based level of regulatory control required to assure safety and effectiveness)
- Class determines pre-market process and required level of support data:
 - ▶ Class I or II: 510(k) (Pre-Market Notification)
 - ▶ Class III: PMA (Pre-Market Application)
- Pre-Market process may require clinical performance data in accordance with Investigational Device Exemption (IDE) regulation
- Key approval determinant: Documented and proven safety and effectiveness

General Product Approval Pathway

- Product Concept
- Product Research and Development
- Product Manufacturing
- Pre-Marketing Meetings with FDA
- Animal Studies for Toxicity and Efficacy
- IDE
- Human Studies for Safety and Efficacy
- PMA or 510(k)
- Labeling Approval
- Establishment Registration
- Post-Marketing Surveillance

Note: In Vitro Diagnostic device (IVD) subject to CLIA and specific labeling

Investigational Device Exemption

An **Investigational Device Exemption (IDE)** allows an unapproved device to be used in the clinical study(ies) that are required to support a pre-market submission. Some types of studies are exempt from IDE regulations.

- An IDE (plus IRB approval) is most likely required for those clinical studies (i.e., significant risk medical device studies) used to support a PMA submission
- 21 CFR Part 812 establishes the process for submitting an IDE and the requirements for conducting the study
- A clinical trial conducted under an IDE must follow GCP regulations:
 - ▶ 21 CFR Part 50 - Protection of Human Subjects
 - ▶ 21 CFR Part 56 - IRB
 - ▶ 21 CFR Part 54 - Financial Disclosure for Clinical Investigators
- Other applicable regulations such as 21CFR11 as appropriate
- Various subparts of the GMP regulation, 21 CFR 820 – Quality System Regulation apply to the medical device being investigated under the IDE

Key Elements: IDE Application

- Cover letter
- Report of prior investigations
- Investigational plan (study protocol)
- Description of methods, facilities and controls used to manufacture, process, pack, store and install the device
- Example of investigator agreement and names and addresses of investigators including enrolling centers and core laboratories
- Names, addresses and chairpersons of all IRBs
- Justification for amount charged for device
- Copies of all labeling for the device
- Copies of all informed consent forms and related information materials to be provided to subjects as required by 21 CFR 50.
- Other information requested by the FDA or previously submitted in pre-IDE process

Sponsor Responsibilities Under IDE

- FDA and IRB Approval
- Select Investigators
- Select Monitors and Monitoring Process
- Device Control
- Investigator Agreement, CV, experience, prior research performance
- Inform Investigators (prior investigation data and investigational plan)
- Sponsor Records: Admin docs, shipment, disposition, all correspondence
- Sponsor Reports
- Specific Labeling as “Investigational Device” with No Promotion
- Full Compliance with Regulations and Study Protocol

<http://www.fda.gov/CDRH/devadvice/ide/approval.shtml>

Pre-Marketing Notification

- A **Premarket Notification, or 510(k)**, is required for new, non-exempt low- or moderate risk medical devices. It usually applies to Class I and II devices.
 - ▶ Demonstrates substantial equivalence to a predicate device in terms of safety and effectiveness related characteristics
 - ▶ Uses the design control requirements of the Quality System Regulation (QSR – 21 CFR 820)
 - ▶ Submitted 90 days prior to marketing

Note: Average fee \$3500 for large company but reduced or free for smaller companies.

<http://www.fda.gov/cdrh/devadvice/314.html>

Pre-Marketing Application

- A **Premarket Application (PMA)** is required to market new and/or high-risk devices. It applies to Class III devices. A PMA includes (among other items):
 - ▶ Complete description of product
 - ▶ Non-clinical data such as animal studies
 - ▶ Summary of all clinical study results e.g., IDE
 - ▶ Design information
 - ▶ Manufacturing information
 - ▶ Labeling
 - ▶ Environmental assessment or Exclusion

<http://www.fda.gov/cdrh/devadvice/pma>

PMA Application Steps

- Filing review
- Statistical review for filing
- Review of manufacturing information for compliance with the Quality System regulation (21 CFR 820).
- PMA filing decision
- Day-100 Meeting
- Quality System Inspection(s) by the FDA field personnel. An FDA manufacturing inspection is conducted for all original PMAs and may be conducted for PMA supplements requesting approval of alternate or additional manufacturing and sterilization facilities.
- Bioresearch Monitoring (BIMO) Audit (audit of clinical study data)

Note: Average fee \$200,000 for large company but reduced or free for smaller companies. Additional fees for supplements and panel track.

PMA Application Steps (continued)

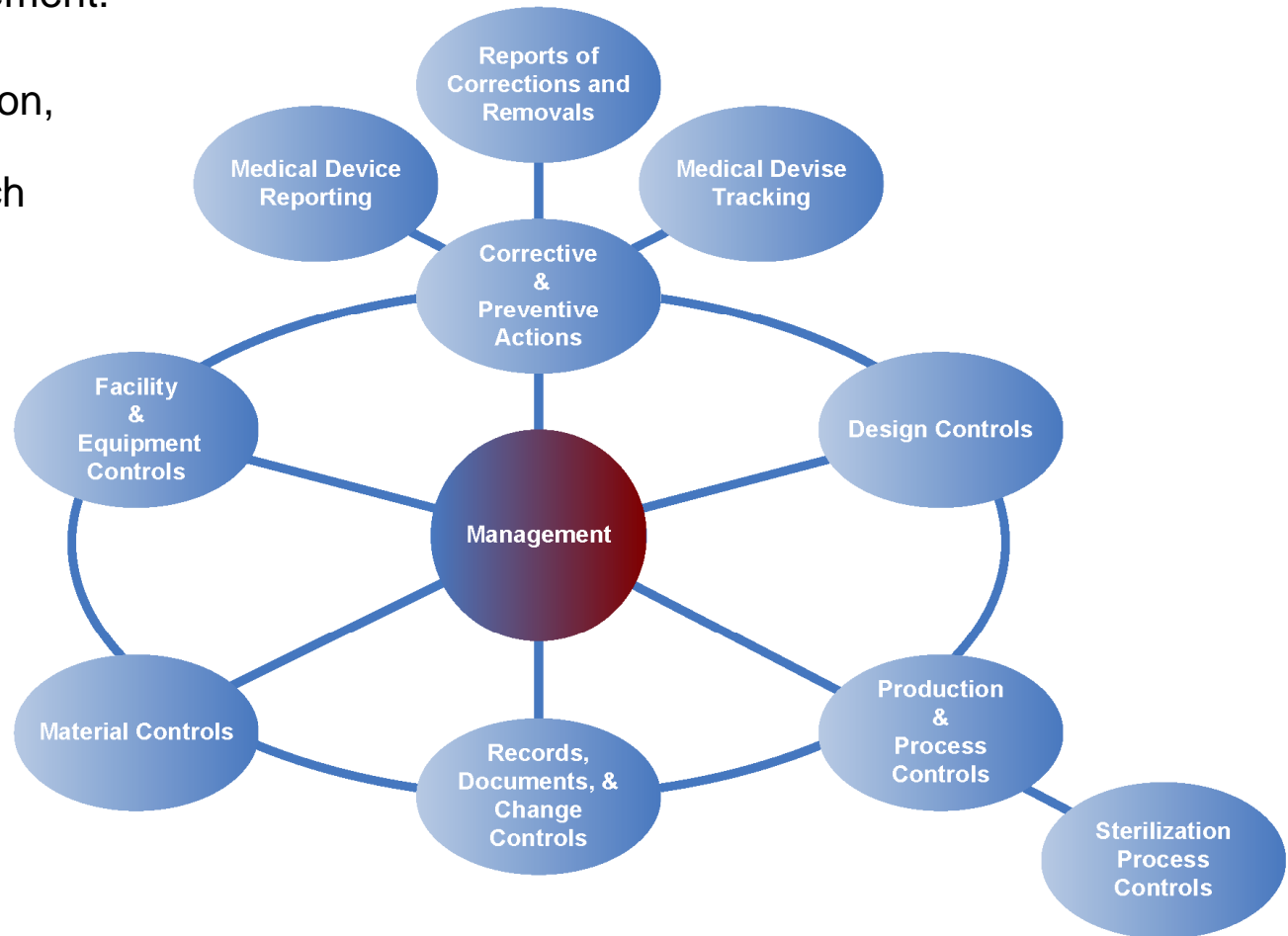
- Substantive review coordination and completion in areas such as:
 - ▶ Preparation of FDA Summary of Safety and Effectiveness Data (SSED)
 - ▶ Non-clinical Studies
[Microbiological, Toxicological, Immunological, Biocompatibility, Shelf Life, Analytical (for IVDs), Animal, Engineering (Stress, Wear, Fatigue, etc.)]
 - ▶ Clinical Studies
- Panel meeting decision, mailing, date (if panel meeting is appropriate)
- Transcripts received, reviewed and placed in administrative record
- QS/GMP clearance
- Final response for GMP/BIMO
- Final decision memo followed by approval package

Note: Standard or Modular Option (180 versus 90 day review cycles)

QSR – 21 CFR Part 820

21 CFR Part 820 defines the requirements for the Quality System under which the medical device is designed (Class III) and manufactured. A Quality System is defined in 820.3(v) as the organizational structure, responsibilities, procedures, processes, and resources for implementing quality management.

The QSR also provides the framework for other information, in addition to the clinical data collected under the IDE, which is required for the pre-market submission (in particular the PMA).

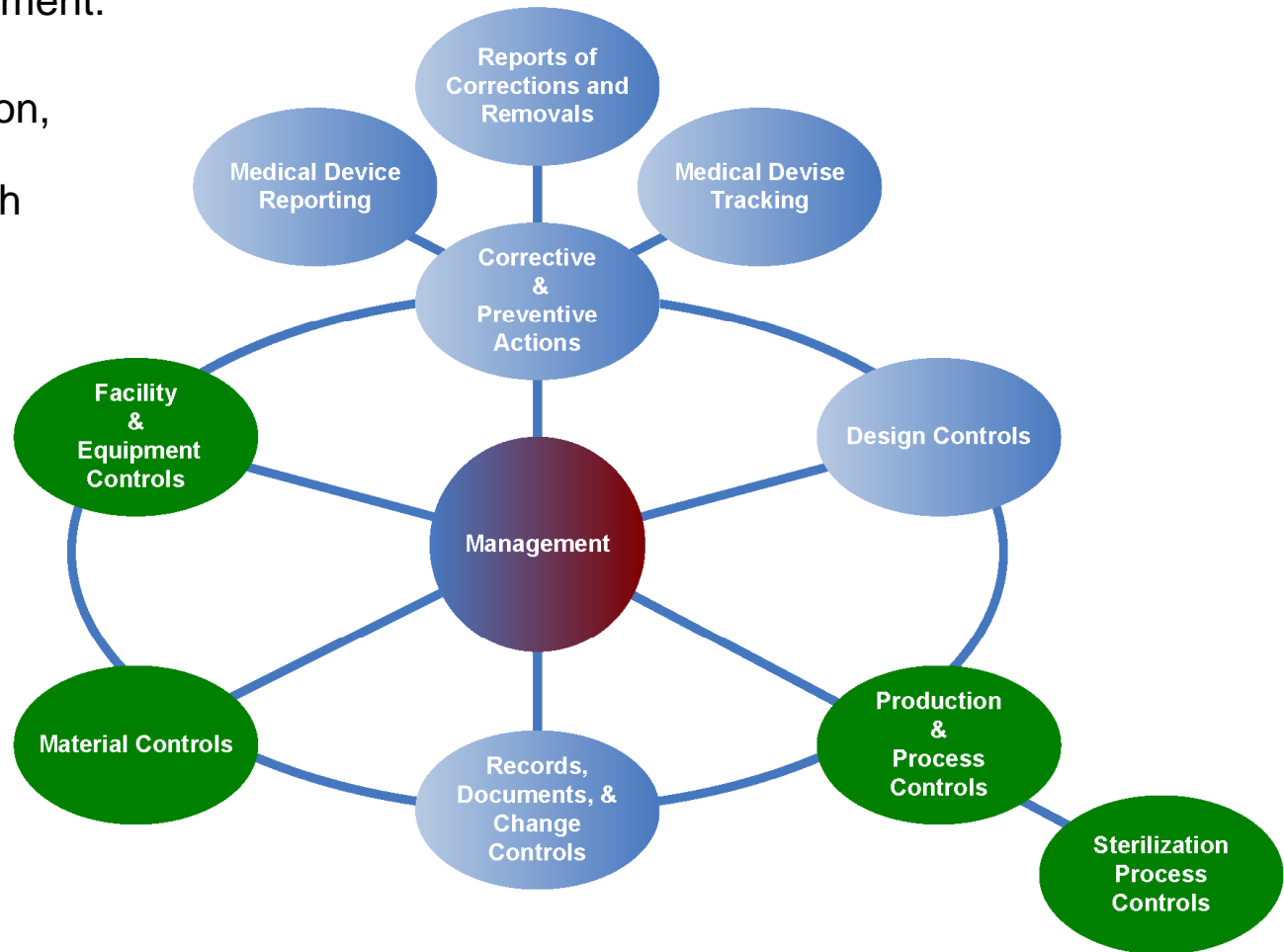


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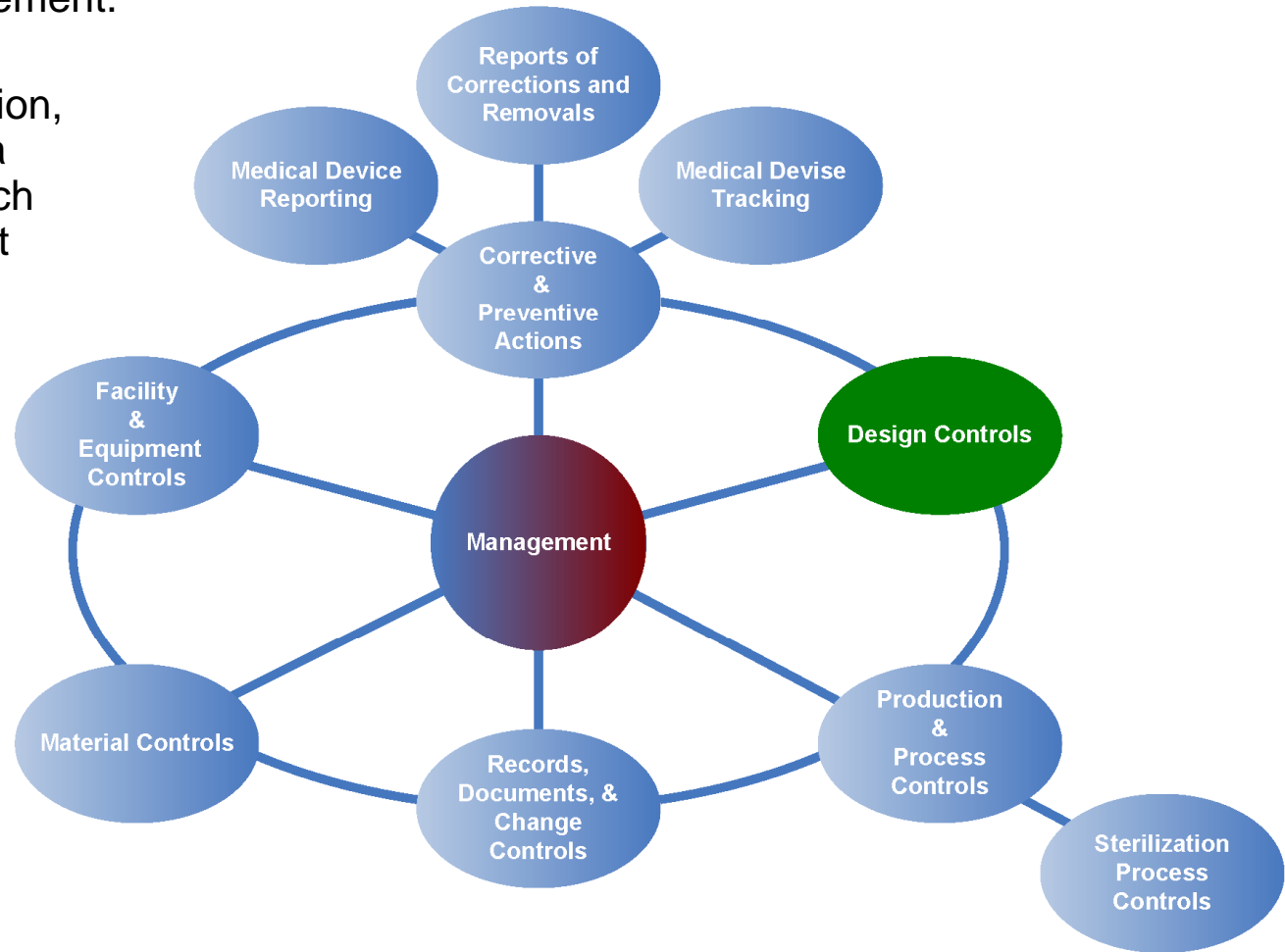
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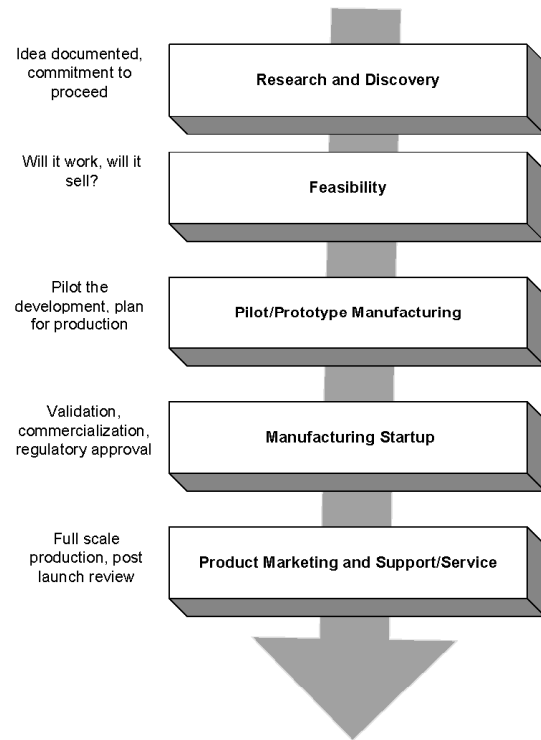
Some Subparts help establish the manufacturing requirements that are provided with the pre-market submission.

Others provide information about the design of the medical device and the processes used to manage design changes.



Design Controls

Product Development Process



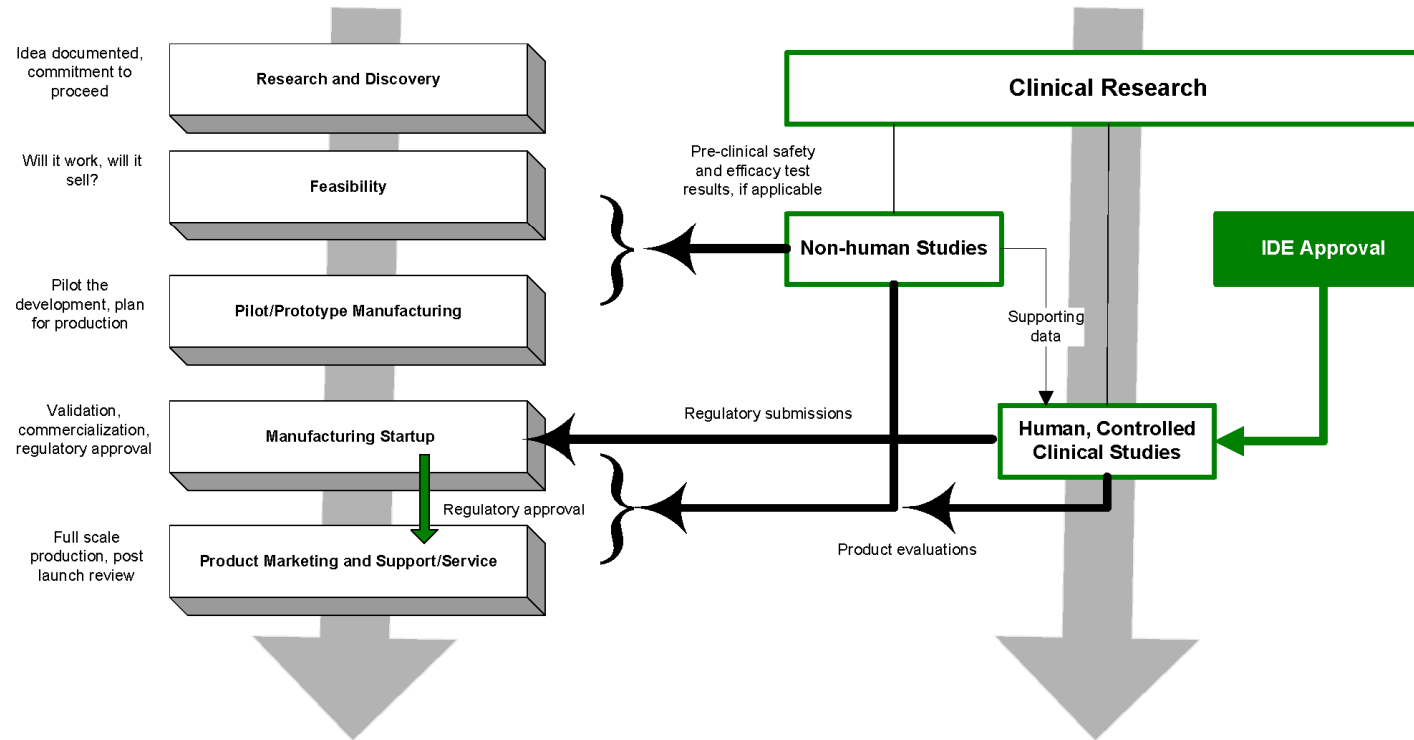
Design Controls are implemented through a Product Development Process that ensures documentation of design inputs, design outputs, design verifications, and change control/phase gate review documentation is accumulated for the Design History File (DHF).

Business Plan/Regulatory Strategy	IRB Report/Approval
Quality Plan	Legal/Patent Clearances Patent Title
Design Input/Output/Verification Matrix	Failure Mode & Effects Analysis (FEMA)
Design/Process Risk Analysis	Lifecycle Study
Commercialization Package	Reliability Study
In-vitro Study	Burn-in report
Toxicology Testing	Software Validation Report
Microbiological Testing	Change Control Records

Product Design Documentation (Design History File – DHF)

Design Controls

Product Development Process



Clinical Research supports the Product Development Process by establishing the safety and efficacy of the medical device.

Business Plan/Regulatory Strategy
Quality Plan
Design Input/Output/Verification Matrix
Design/Process Risk Analysis
Commercialization Package
In-vitro Study
Toxicology Testing
Microbiological Testing

IRB Report/Approval
Legal/Patent Clearances Patent Title
Failure Mode & Effects Analysis (FEMA)
Lifecycle Study
Reliability Study
Burn-in report
Software Validation Report
Change Control Records

Human Use Clinical
Marketing Clinical
Consumer Use/Preference Study
Pre-market Submission (510(k), PMA)

Product Design Documentation (Design History File – DHF)

Summary

- Regulatory plan
 - ▶ Communicate honestly, frequently and early with the FDA
 - ▶ Develop realistic expectations of FDA
 - ▶ Maintain full understanding of current regulations and requirements
- FDA approval does not equal third party payor approval
 - ▶ Include device and medical procedure cost
- Conflict of interest
- Patent and intellectual property agreement
- Strategic business plan and model:
 - ▶ Map to development, marketing and post-marketing, export
 - ▶ Financial requirements with clear presentation of device and significance
- Post-marketing
 - ▶ Quality system, medical device reporting, device tracking
 - ▶ Surveillance study may be required by FDA

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