AdvaMed
Advanced Medical Technology Association

IVD Regulation Overview

Requirements to Assure Quality & Effectiveness

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Statutory and Regulatory Requirements

- Statute:
  - Food, Drug, and Cosmetic Act
  - Food and Drugs Act of 1906
  - Food and Drug Administration Modernization Act
- Regulations:
  - *Current Good Manufacturing Practices (QSR)
  - *Submissions (510(k), PMA, BLA)
  - Medical Device Reporting
  - Labeling
  - Establishment Registration and Device Listing
  - Removals and Corrections

FDA Regulatory Authority

- Before Market Introduction
  - Clear or Approve information for Safety & Effectiveness
- Manufacturing Processes
  - Conforms to a Quality System (Higher risk products require pre-approval of process)
- While on the Market
  - Monitor complaints/inquiries
  - Trend service history
  - Track potential for serious injury

Current Good Manufacturing Practice

cGMP or
Quality System Regulation (QSR)

Principles of a Quality System

- An integrated process that requires:
  - Planning
  - Commitment
  - Actions
  - Follow up
- Harmonized with ISO 9001

Quality System Regulation

- Management Responsibility
- Design Controls
- Document Controls
- Purchasing Controls
- Identification and Traceability
- Production and Process Controls
- Acceptance Activities

Quality System Regulation (continued)

- Non-conforming Product
- Corrective and Preventive Action
- Labeling and Packaging Control
- Handling, Storage, Distribution, and Installation
- Records
- Servicing
- Statistical Techniques

Management Responsibility

- Quality Policy
  - Assure organizational structure can meet Quality objectives
  - Assess risk to patient, user, and business
- Quality System Review
  - Effectiveness of the Quality System

Management Responsibility (continued)

- Quality Audits
  - Determine the effectiveness of the Quality System
  - Internal and External (FDA Inspections)
- Personnel
  - Understanding of *their* impact on product performance and Quality
- *Reiterate*: Management is accountable
  - Potential civil & criminal penalties

Design Controls

- Define user requirements
  - Safe and effective for intended use, ergonomic needs of user, etc.
- Translate into design specifications (design inputs)
  - Include performance, reliability, compliance to standards/regulations, environmental conditions, etc.
- Design and develop the product
- Perform risk assessment
- Verify and Validate product

Design Controls: Risk Assessment

Failure Mode & Effects Analysis (FMEA)

- Probability v. Severity
- Propose mitigation
- Assess acceptability

Prospective, Best Guess

Probability of Occurrence Estimate	Severeness Category		
	Minimal (1)	Moderate (2)	Severe (3)
Remote (A)	1A	2A	3A
Occasional (B)	1B	2B	3B
Frequent (C)	1C	2C	3C

- Acceptable
- Undesirable… management review required
- Unacceptable… redesign or alternative strategy required

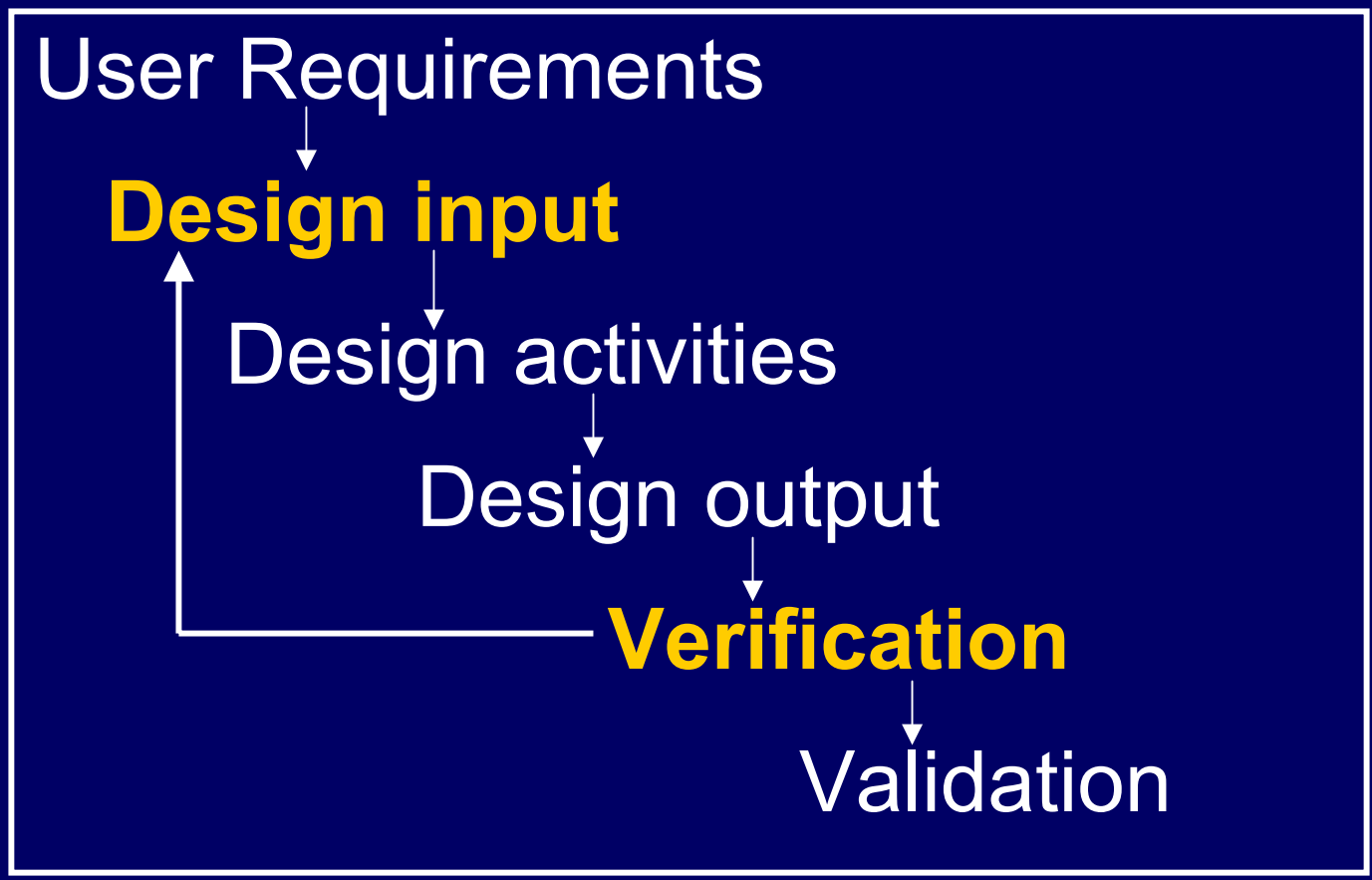
Design Controls: Management Review

- Evaluate health
- Evaluate business risks
- Evaluate manufacturability; Can it be made?
- Conduct several reviews during product design and development

Design Controls: Verification

- Procedure for verifying that the design outputs meet the design inputs, i.e. that the device performs as was intended

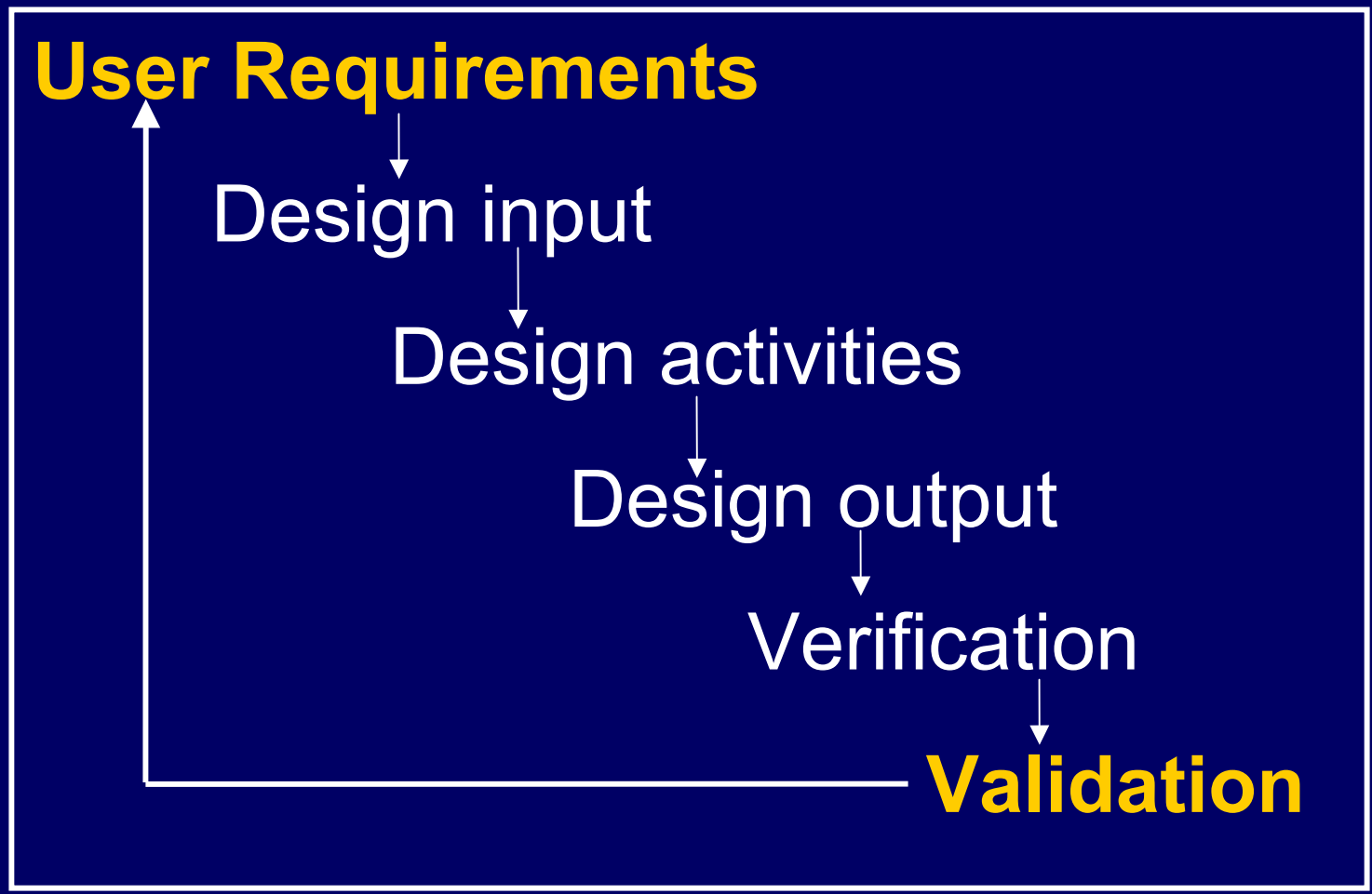
Design Control



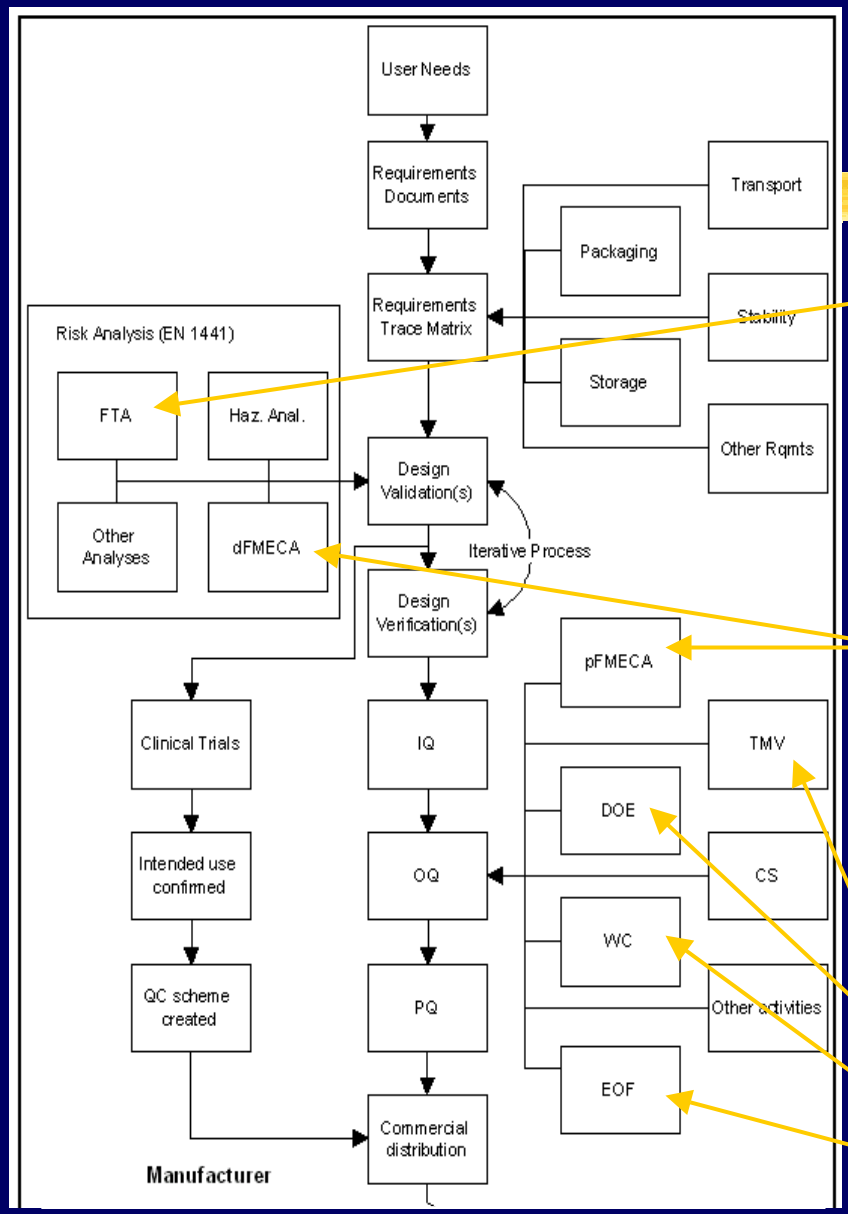
Design Controls: Validation

- Procedures for testing the device under actual (or simulated) operating conditions on initial production units

Design Control



Example of Verification & Validation of a Product



FTA: Fault Tree Analysis (Top down method used to analyze a failure e.g. shock could be a potential failure, analyze what parts of the product could cause a shock)

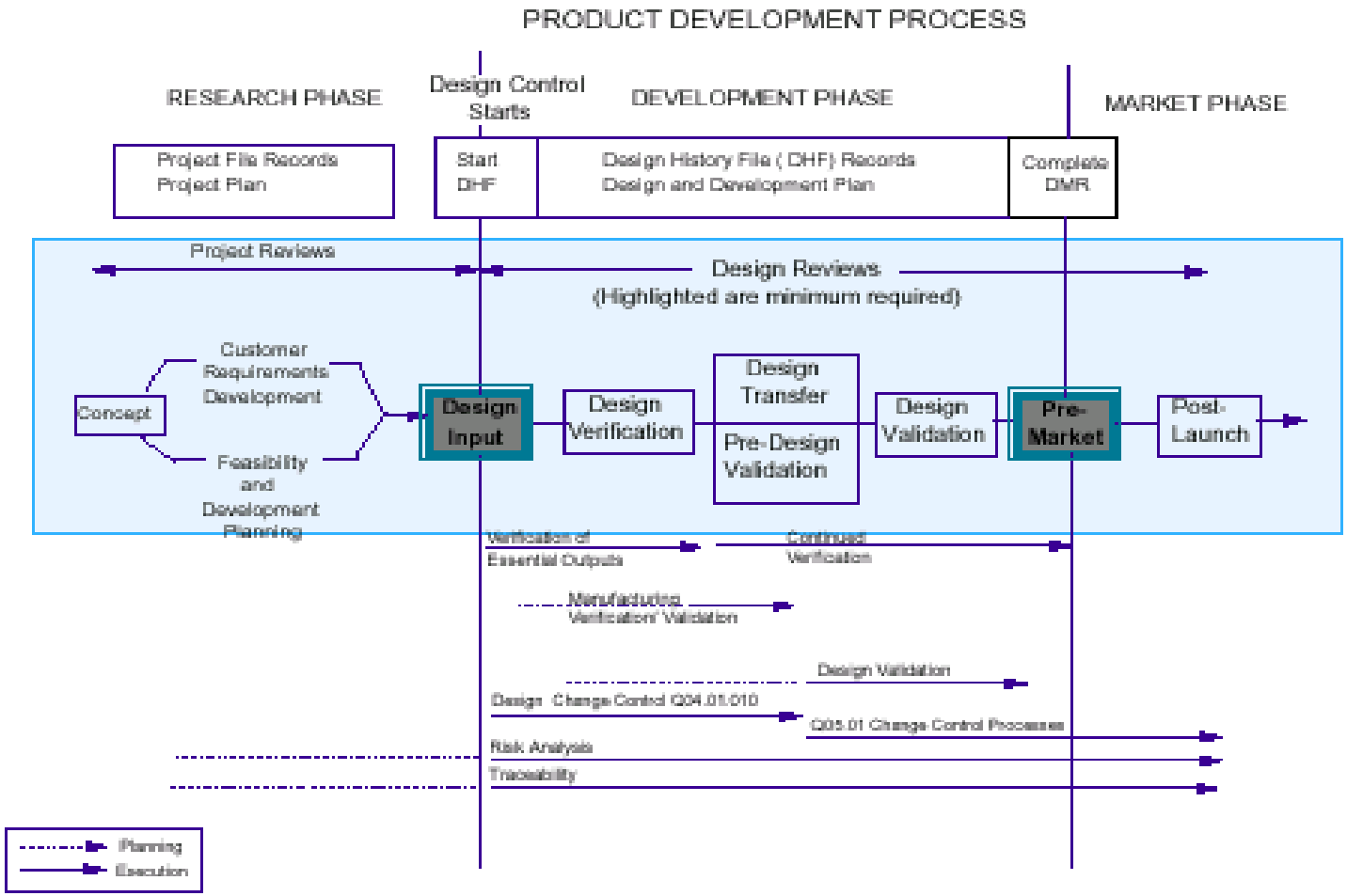
FMECA: Failure Modes, Effects, and Criticality Analysis (Bottom-up method where basic failures are examined to determine their ultimate effect, e.g. effect of a circuit part shorting out)

TMV: Test Method Validation
DOE: Design of Experiments
WC: Worst case
EOF: Edge of failure

Design Controls: Transfer

- Procedures to ensure that the device design is correctly translated into production specifications
  - Objective: To assure *current* Good Manufacturing Practices (cGMP) are achieved

Design and Development Process: an example



Design Controls: Deliverables

- Design History File
- Device Master Record
  - "Recipe" to manufacture

Document Controls

- Documents that are put in place to accomplish cGMP, e.g.,
  - DHF: Design History File: Record of design activities
  - DMR: Device Master Record: All procedures, parts, and specifications used for manufacturing the device
  - DHR: Device History Record: Records containing the production history of each device or lot

Document Controls (continued)

- Changes must be:
  - Documented with reason and justification for the change
  - Version controlled
  - Approved before use by management
  - Training completed
  - Obsolete versions taken from circulation
  - Reviewed periodically

Purchasing Controls

- Purchased supplies must conform to specified requirements
  - Incoming specifications
  - Incoming quality control

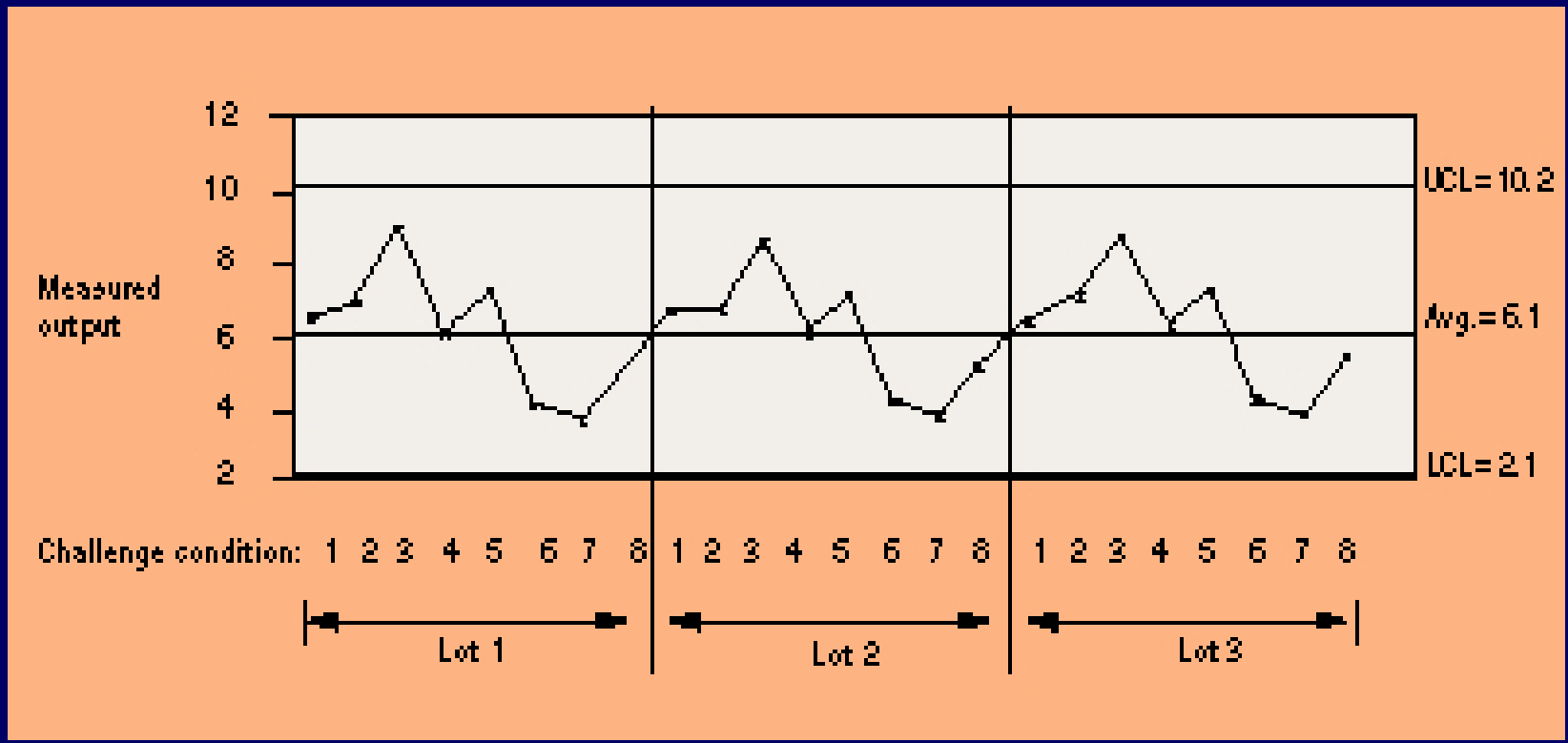
Identification and Traceability

- Identification during all stages of receipt, production, distribution, and installation
- Identification by serial number or lot number, to facilitate CAPA

Production and Process Controls

- Monitor processes to ensure conformance to specifications
  - Instructions
  - Monitoring control parameters
  - Qualification of equipment

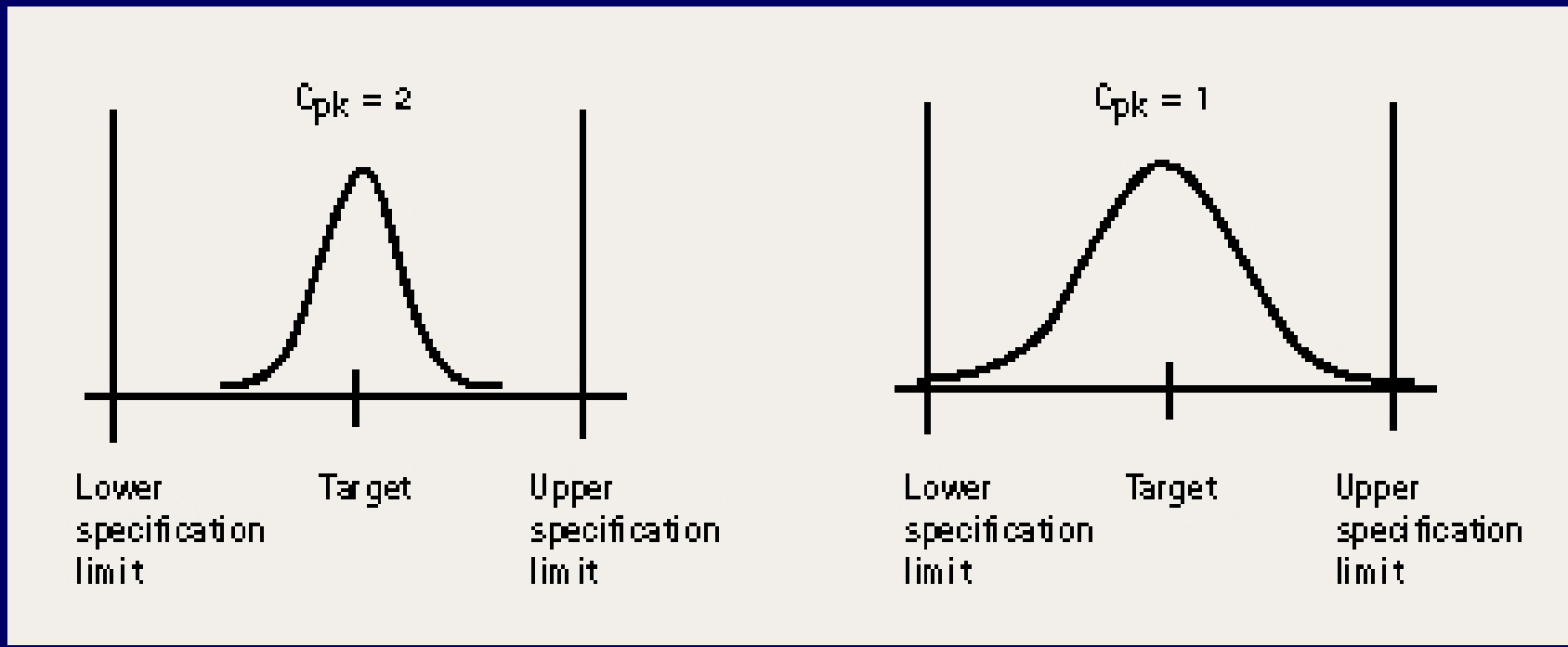
Process Control



Three lots within conformance; within the Upper and Lower Control Limits (UCL & LCL)

Weese & Buffaloe, MDDI 1998;20

Process Control



Process capability (C_{pk}) blends statistical results with process specifications. A process with a C_{pk} of 2 (left) is more capable than one that has a C_{pk} of 1 (right).

Weese & Buffaloe, MDDI 1998;20

Production and Process Controls (continued)

- Changes must be evaluated according to risk:
  - to patient
  - to user
  - to business
- Changes must be verified and/or validated before approval and implementation

Production and Process Controls (continued)

- Procedures for health and cleanliness of the workers and the environment
- Prevention of contamination

Acceptance Activities

- Receiving, in-process, and finished device acceptance, e.g.,
  - Inspect, test, verify incoming product conformance
  - Batch records must contain data that meet pre-determined specifications
  - Must conform to the Device Master Record (DMR)

Non-conforming Product

- Identify product not meeting specification
- Disposition must be documented
- *Follow up* evaluations are required (Deviation Reports)

Corrective and Preventive Action (CAPA)

- Applies to:
  - factory problems
  - audit findings
  - design
  - service
  - complaints
  - returned product

Complaint Definition

- Any allegation of deficiency related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a device

Complaints

- *Every* valid complaint must be reviewed and evaluated
- Evaluate if complaint is a Medical Event (potential to cause serious injury) and report to FDA
- Each complaint is associated with a corrective action
  - Both complaints and service records are tracked

CAPA Process

- Investigate the cause
- Report to FDA if required
- Correct the problem (Corrective Action) and prevent recurrence (Preventive Action)
- Check effectiveness of the corrective action
- Approve and implement preventive action
- Monitor long term (as necessary)

Compliance to the Quality System (QSR)

- FDA audits all manufacturing sites
- Integrity of the Quality System is evaluated
- Complaint resolution and CAPA are major components

Senior management is *accountable* for establishment & maintenance of an effective Quality System

FDA Submissions

- CDRH (Center for Devices and Radiological Health)
  - Exempt of submission
  - 510(k) (Clearance)
  - PMA (Pre-market approval)
- CBER (Center for Biologics Evaluation and Research)

All products must follow cGMP

510(k)

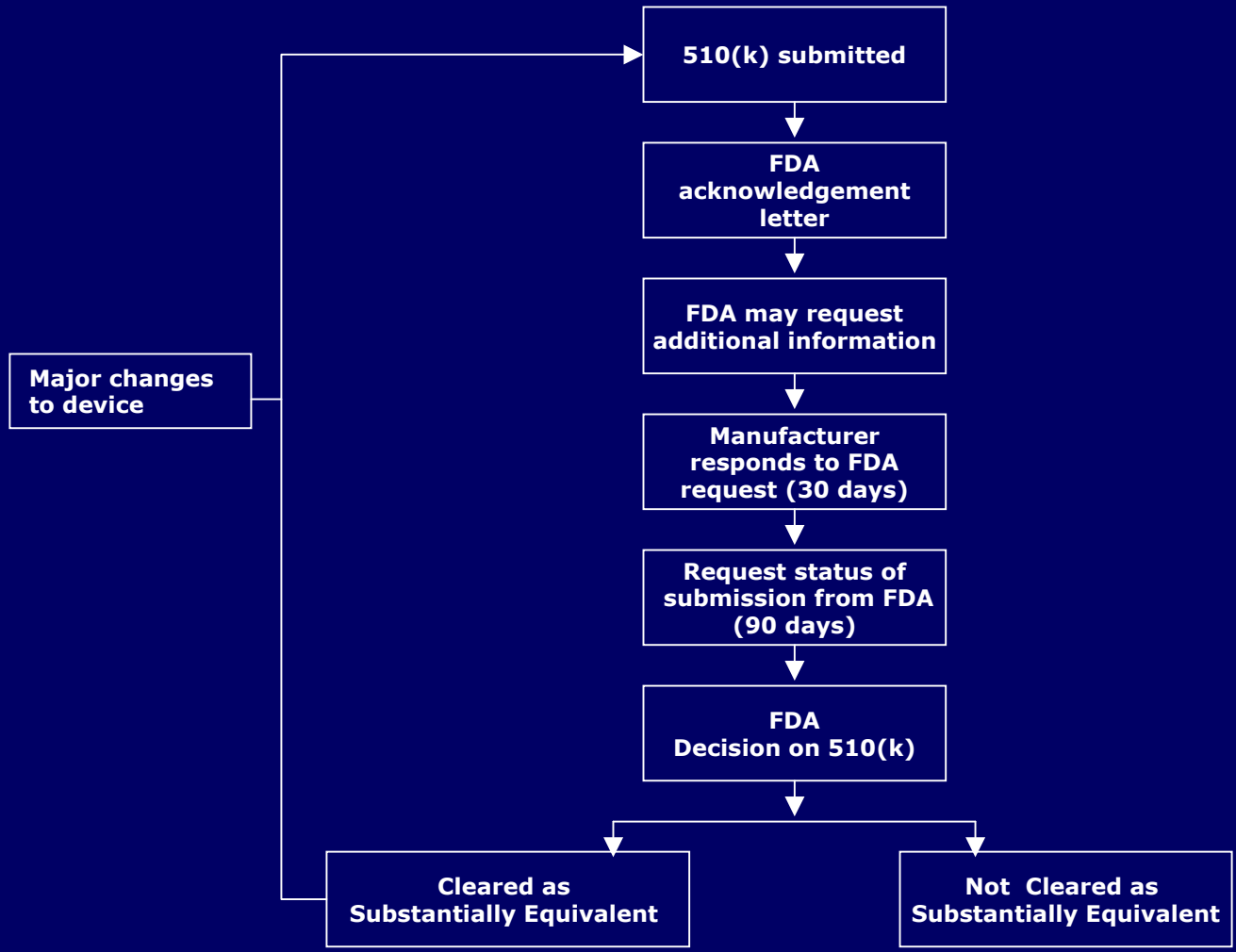
- Establish substantial equivalence to a legally marketed predicate device
  - Same or similar intended use as predicate
  - Same technological characteristics (design, materials, technology) as compared to the predicate device ("me too") or, if different….

Must be *as* safe and effective

Elements of a 510(k)

- Name and address of manufacturer
- Device name and Device listing classification
- Device Description of intended use and directions for use
- Comparison to predicate device
- Truthful and accurate statement (accountability)
- Summary of safety and effectiveness
- Performance data that supports product claims
- Conformance to standards
- Labeling
- Software certification statement, if applicable
- Predicate device labeling, if available

The 510(k) Process



Pre-Market Approval (PMA)

- Highest risk devices
  - Prove safety and effectiveness of device
  - Examples:
    - Hepatitis markers for diagnosis
    - Estrogen receptors
    - New technology
    - Analyte new to FDA

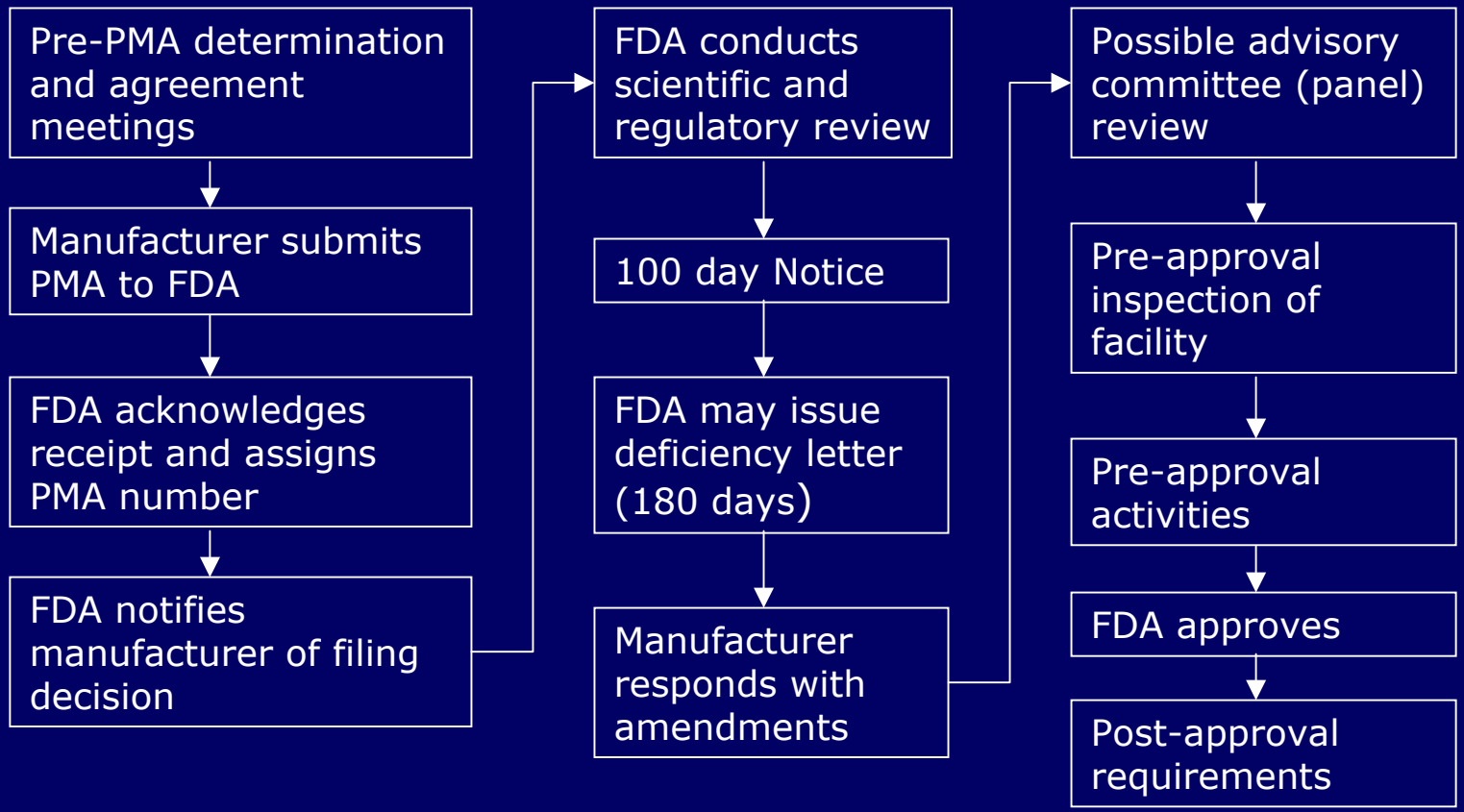
Elements of PMA

- More involved submission
  - Name and address of manufacturer
  - Table of contents
  - Summary of safety and effectiveness
    - Indications for use
    - Alternative practices and procedures
    - Marketing history
    - Summary of studies
    - Conclusions drawn from studies
  - Complete device description

Elements of a PMA (continued)

- Reference to applicable performance standards
- Results of non-clinical and clinical studies
  - Clinical studies can involve tens of thousands of samples at multiple sites
- Bibliography of all published reports
- Sample, if requested
- Labeling
- Environmental assessment (unless qualified for exclusion)
- Other FDA requests

PMA Process


Pre-PMA determination and agreement meetings
Manufacturer submits PMA to FDA
FDA acknowledges receipt and assigns PMA number
FDA notifies manufacturer of filing decision
FDA conducts scientific and regulatory review
100 day Notice
FDA may issue deficiency letter (180 days)
Manufacturer responds with amendments
Possible advisory committee (panel) review
Pre-approval inspection of facility
Pre-approval activities
FDA approves
Post-approval requirements

PMA Post-market notifications

- Submitted to FDA
  - PMA Supplement
    - Major changes to safety or effectiveness requires 3-6 months wait before implementing
  - Special Supplement
    - Additional precautions or warning requires a 3 month wait before implementing
  - Annual Reports
    - All other changes throughout year not affecting safety or effectiveness of the product

Key Points

- IVDs are regulated by numerous statutes and regulations from beginning to end
- The manufacturer is required to maintain a Quality System that is audited by the FDA for all devices
- Higher risk devices require submission of more supportive information to demonstrate safety and effectiveness

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