Section 5:
Quality Systems Regulation (QSR) and Good Manufacturing Practice (GMP)
Quality Systems Regulation (QSR)
Quality Systems Regulation (QSR) and Good Manufacturing Practice (GMP)

- Sets of checks and balances to assure safe and effective finished products

- In QS Regulation, FDA has identified the essential elements that a quality system shall embody for
  - design,
  - production, and
  - distribution

- QS Regulation leaves some leeway to manufacturers as to how to implement their specific system

- The FDA monitors device problem data and inspects the operations and records of device device developers and manufacturers to determine compliance with the GMP requirements in the QS regulation
Contents of Quality Systems Regulation

- Quality Systems (QS) Regulation contained in Title 21 Part 820 CFR

- QS Regulation covers:
  - Quality Management and Organization
  - Device design
  - Buildings
  - Equipment
  - Purchase and handling of components
  - Production and process controls
  - Packaging and labeling control
  - Device evaluation
  - Distribution
  - Installation
  - Complaint handling
  - Servicing
  - Records
GMP Regulation and its Requirements

- Good Manufacturing Practice (GMP) requirements set forth in QS Regulation are promulgated under section 520 of the FD&C Act.

- GMP require that domestic or foreign manufacturers have a quality system for the:
  - design
  - manufacture
  - packaging
  - labeling
  - storage
  - installation
  - servicing

  of medical devices intended for commercial distribution in the US.

- The GMP regulation requires:
  - that various specifications and controls be established for devices
  - that devices be designed under a quality system to meet these specifications
  - that devices be manufactured under a quality system
  - that finished devices meet these specifications
  - that devices be correctly installed, checked, and serviced
  - that quality data be analyzed to identify and correct quality problems
  - that complaints be processed

Source: FDA, 2006
Types of Establishments subject to the GMP

- Remanufacturers
- Custom Device Manufacturers
- Contract Manufacturers
- Contract Testing Labs
- Repackagers, Relabelers, and Specification Developers
- Manufacturers of Accessories
- Initial Distributors
Example Element of GMP: Design Controls

- Under Design Controls
  
  - The design needs to be reviewed throughout development to make sure all requirements are being met.
  
  - Manufacturers must
    
    - establish performance requirements for a device before production,
    
    - ensure that device components are compatible with each other,
    
    - select adequate packaging materials, and
    
    - where appropriate do a risk analysis.

Source: FDA, 2006
Design Controls Example 1: Defibrillator for Use in Hospitals and Ambulances

• If a manufacturer were planning to design a new defibrillator for use in hospitals and ambulances to restart the heart in emergencies, designers would have to consider all aspects of use in both settings, not just in the hospital:
  – Storage temperatures in the ambulance
  – Road shock and vibration
  – Two-way radio interference
  – Electrical noise generated by the siren
  – Others…

• Under Design Controls, the design needs to be reviewed throughout development to make sure all requirements are being met
Design Controls Example 2: Glucose Monitor for Home Use

• If a manufacturer were planning to design a glucose monitor for use by diabetics to monitor their blood glucose at home, designers would have to consider special circumstances that might arise, such as

  – use by diabetics who have diabetic eye disease,
  – use by other persons in the home and medical personnel

They would also have to consider the effects on the monitor from

  - other electrical and electronic products in the home such as computers, televisions, radios, telephones and other medical devices
QSR Documentation Requirements

I. General (Non-device-specific)
Quality System Report Documents

- Used for many activities that are essential to operating a manufacturing establishment; these documents are not specific to any given product
- Contain **standard operating procedures (SOP’s)** and **standard quality assurance procedures (QAP’s)**
- Typical documents that can be contained in the general record:

<table>
<thead>
<tr>
<th>Document Type</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Employee training procedures</td>
<td>Supplier assessment policy</td>
</tr>
<tr>
<td>Cleaning procedures</td>
<td>General design control procedures</td>
</tr>
<tr>
<td>Insecticide userremoval procedures</td>
<td>Component inspection procedures</td>
</tr>
<tr>
<td>Air conditioning/heating procedures</td>
<td>Workmanship standards</td>
</tr>
<tr>
<td>Tool kit policy</td>
<td>Design review policy/procedure</td>
</tr>
<tr>
<td>Safety procedures</td>
<td>Label review policy/procedure</td>
</tr>
<tr>
<td>Procurement procedures</td>
<td>Sterile water system maintenance</td>
</tr>
<tr>
<td>Returned goods policies</td>
<td>Calibration policy</td>
</tr>
<tr>
<td>Drawing numbering system</td>
<td>Complaint handling procedure</td>
</tr>
<tr>
<td>Change control procedure</td>
<td>Recall procedure</td>
</tr>
<tr>
<td>Service policy</td>
<td>Deviation review policy/procedure</td>
</tr>
</tbody>
</table>

Source: FDA, 2006
QSR Documentation Requirements

II. Device-specific
Device Master Record (DMR)

- Device master record (DMR) is the term used for all of the routine documentation required to manufacture devices that will consistently meet company requirements.

- Compilation of records containing the procedures and specifications for a finished device:
  - shows and/or tells employees how to perform specific functions related to the production of a device.

- DMR Contents:
  - Device Specification
  - Specific documents (drawings, procedures, labels, data forms, etc., for a specific product or family of products)
  - (Records for In Vitro Diagnostic Products)

Source: FDA, 2006
DMR: A Central Element of the Development and Production Cycle

DMR: Device Master Record
DHF: Design History File

Source: FDA, 2006
## Typical Location of Documents in a DMR

<table>
<thead>
<tr>
<th>TYPE OF DMR ELEMENT</th>
<th>ORIGINALS</th>
<th>WORKING COPIES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reference list(s)</td>
<td>Engr. master file</td>
<td>Manuf. or Procurement</td>
</tr>
<tr>
<td>Component drawings</td>
<td>Engr. or Manuf. Engr. master file</td>
<td>Receiving department</td>
</tr>
<tr>
<td>Component acceptance procedures</td>
<td>SOP master file</td>
<td>Marketing or Engineering</td>
</tr>
<tr>
<td>Device Input specifications (final version)</td>
<td>Engr. master file</td>
<td>Manufacturing</td>
</tr>
<tr>
<td>Manufacturing procedures</td>
<td>Engr. or Manuf. Engr. master file</td>
<td>Manufacturing</td>
</tr>
<tr>
<td>Test specifications</td>
<td>Engr. master file</td>
<td>Engr. or Manuf. Engr.</td>
</tr>
<tr>
<td>Test procedures</td>
<td>Engr. or Manuf. Engr. master file</td>
<td>Manuf., QA, QC or Final Test</td>
</tr>
<tr>
<td>Inspection procedures</td>
<td>Manuf., QC, or SOP master file</td>
<td>Manufacturing or QC</td>
</tr>
<tr>
<td>Label drawings</td>
<td>Engr. master file</td>
<td>Engr., QA, or Manuf.</td>
</tr>
<tr>
<td>Label artwork</td>
<td>Artwork master file</td>
<td>Engr., Procurement</td>
</tr>
<tr>
<td>Label control procedures</td>
<td>Manuf., QC, or SOP master file</td>
<td>Manufacturing</td>
</tr>
<tr>
<td>Specific cleaning procedures</td>
<td>SOP master file</td>
<td></td>
</tr>
<tr>
<td>General cleaning procedures</td>
<td>QSR master file</td>
<td></td>
</tr>
<tr>
<td>System audit procedures</td>
<td>QSR master file</td>
<td></td>
</tr>
<tr>
<td>Employee training procedures</td>
<td>QSR master file</td>
<td></td>
</tr>
</tbody>
</table>

SOP = Standard Operating Procedure  
QSR = Quality System Record  
QA = Quality Assurance  
QC = Quality Control  

Source: FDA, 2006
Sample specification excerpt: Performance Characteristics for Defibrillator

5.0 PERFORMANCE CHARACTERISTICS
5.1 DEFIBRILLATOR OUTPUT

5.1.1 Waveform: Monophasic pulse (Edmark Waveform)

*5.1.2 Energy Range: 10-320 joules delivered into a 50 ohm load.
   D320/320W
   Energy Range: 10-400 joules delivered into a 50 ohm load.
   D400/400W

*5.1.3 Energy Accuracy:
   DELIVERED ENERGY INDICATOR OR AUTO 320 (400)
   and AUTO 160 (200) push-buttons
   Error less than 10% or 4 joules, whichever is greater, into 50 ohms and 25% or 4 joules, whichever is greater, into a 25 to 100 ohm load when measured in accordance with XXX recommendations.

5.1.4 Pulse Width:
   into 95% of the energy delivered in <5 ms 50 ohm load.

5.1.5 Charge Time:
   (D320/320W)
   Charge Time: 10 sec. max.
   8.5 sec. typical.
   (D400/400W)
   Charge Time: 12 sec. max.
   10.5 sec. typical.

5.1.6 Pulse Rate:
   <5

5.1.7 Energy Loss Rate:
   <15% in 30 seconds.

5.1.8 Charge Dump Time
   <25 volts left in 4 seconds and <2 joules in 3 minutes after activation of capacitor dump circuit.

Source: FDA, 2006
Document and Change Control
• Oftentimes, changes or modifications are performed on a device or its associated processes. Any such change needs to be documented in the DMR ("Change Control").

• The burden is on the manufacturer to determine whether the change/modification significantly changes the safety or effectiveness profile of a device. In case of a significant change, a 510(k) or PMA supplement must be submitted to FDA depending on the classification of the device. Additional submissions are not required for marketing or convenience changes where safety or effectiveness could not be significantly affected.

• A solid Change Control Process is an essential part of a manufacturer’s Quality System!
Medical Device Reporting
Complaint Handling and Medical Device Reporting (MDR)

- GMP regulation gives clear advise of
  - how complaints should be handled (Complaint Handling System)
  - how responsibilities should be assigned
  - how device failure analysis should be performed
  - what sources of information a manufacturer should use to detect device problems

- In addition to the GMP requirements, device manufacturers need to also comply with the Medical Device Reporting (MDR) regulation (21 CFR 803)
  - All manufacturers of medical devices are required to “notify FDA when they become aware of a death or serious injury that may have been caused or contributed to by one of their marketed devices and/or any malfunction of one of their devices which, if it were to recur, would be likely to cause or contribute to a death or serious injury.”
  - Specific time limits for reporting exist (30 calendar days for any report of a device-related death, serious injury, and malfunction)

Source: FDA, 2006
FDA’s Quality System & Global ISO Standards
Relationship between FDA’s Quality System Regulation and global ISO Standards

- FDA’s Quality System Regulation Part 820 is harmonized with ISO 13485:2003, which is based on ISO 9001:2000.

- ISO 13485 contains requirements for medical device manufacturers in addition to the general quality system requirements found in ISO 9001.

- FDA harmonized their QSR with the ISO standards, because many other countries rely on ISO standards in regulating medical devices. Benefit: Agencies can more readily rely on one another’s inspections and exchange inspection reports.

- Global Harmonization Taskforce actively pursues harmonization.
Useful Resource 1: FDA’s Medical Device Quality Systems Manual

Contents

Foreword ii
Preface iii
Abstract iv
Note to Manufacturers of Medical Devices v

1. The Quality System Regulation 1-1
2. Quality Systems 2-1
3. Design Controls 3-1
4. Process Validation 4-1
5. Personnel 5-1
6. Buildings and Environment 6-1
7. Equipment and Calibration 7-1
8. Device Master Record 8-1
9. Document and Change Control 9-1
10. Purchasing and Acceptance Activities 10-1
11. Labeling 11-1
12. Product Evaluation 12-1
13. Packaging 13-1
14. Storage, Distribution and Installation 14-1
15. Complaints 15-1
16. Servicing 16-1
17. Quality Systems Audits 17-1
18. Factory Inspections 18-1

Appendixes
Quality System Regulation 19-1
Application of the Medical Device GMPs to Computerized Devices and Manufacturing Processes 19-21

Available for download at: http://www.fda.gov/cdrh/dsma/gmpman.html
Useful Resource 2: Global Harmonization Task Force (GHTF) website

www.ghtf.org

General Information

Summary Statement

The Global Harmonization Task Force (GHTF) is a voluntary group of representatives from national medical device regulatory authorities and the regulated industry. Since its inception, the GHTF has been comprised of representatives from five founding members grouped into three geographical areas: Europe, Asia-Pacific, and North America, each of which actively regulates medical devices using their own unique regulatory framework.

The purpose of the GHTF is to encourage convergence in regulatory practices related to ensuring the safety, effectiveness/performance, and quality of medical devices, promoting technological innovation and facilitating international trade, and the primary way in which this is accomplished is via the publication and dissemination of harmonized guidance documents on basic regulatory practices. These documents, which are developed by four (4) different GHTF Study Groups, can then be adopted/implemented by member national regulatory authorities. The relationships between the work of each Study Group can be represented schematically.

The GHTF also serves as an information exchange forum through which countries with medical device regulatory systems under development can benefit from the experience of those with existing systems and/or pattern their practices upon those of GHTF founding members.

GHTF Procedural Documents

- GHTF Roles and Responsibilities (PDF) (Word)
- GHTF Guiding Principles (PDF) (Word)
- GHTF Operating Procedures (PDF) (Word)
- Document Format & Style Guide (Word)
- Document Template (see Document Format & Style Guide for installation instructions)

Source: GHTF, 2006