

# GxP for Manufacturing

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# Congratulations!

- You have developed a great product
- Now you're ready for manufacturing
- What should you be thinking about?

# You have to manage the risk

- Even a great product can result in injury, death, recalls ... and perhaps shutting down your company.



# Examples

- Peanuts – Company went bankrupt
- B&L Renue Lens Solution – Stock Price decline
- Hydroxycut – Liver damage
- Original Swine Flu vaccine – 1978 nerve effects
- DDT – Killed birds
- Vioxx – Killed patients

News at 5:00

Law suits at 11:00

# The FDA holds YOU responsible

- In your manufacturing facility – OR –
- Outsource to a contract manufacturer
- Large chains requiring proactive 3<sup>rd</sup> party audits of suppliers of their private label products
  - CVS
  - Target
  - WalMart

# The FDA can inspect you

- Issue 483 Reports for violations
  - Public record
- Can force recalls &/or shut you down
- But they are understaffed
  - Random audits
  - Auditor's focus varies
  - Complaints are always followed up
- You are **STILL** responsible

# GMPs (Good Mfg Practices)

- Defined to ensure product safety
- Controls based on product risk
- Biomedical
  - 21 CFR Part 210/211      Drugs
  - 21 CFR Part 820      Medical Devices
- Computer systems (all products)
  - 21 CFR Part 11

# Drugs - requirements

- A Quality System - *documented*
  - Quality System Manual
  - Independence, Authority & Training
  - Annual Product Reviews
  - Internal Audits
  - CAPA System
  - Complaint Handling (FDA reporting, retains required)
  - Failure/Deviation Investigations
  - Change control (SOPs, production)
  - Rework/reprocessing
  - Recalls/returns/salvages
  - Stability testing (container orientation, environment)
  - Validation (cleaning, processes)

# Drugs – requirements (cont'd)

- Facilities & Equipment
  - Flow, waste, chemicals, pest control, etc.
  - Plant and equipment design
  - IQ/OQ/PQ for equipment
  - Sanitation & maintenance
- Material control
  - Receipt & inspection (or vendor qualification)
  - Identification & traceability
  - Control & release
  - Nonconforming material

# Drugs – requirements (cont'd)

- Production System
  - Process change control system
  - Batch production records
  - Equipment qualification & maintenance
  - Retains/Reserve samples
  - Stability testing – container orientations
- Packaging system
  - Validation, cleaning, contamination
  - Label control

# Drugs – requirements (cont'd)

- Laboratory
  - Personnel qualification
  - Methods & procedures
  - Chemicals, standards & solutions handling
  - Logbooks – control & retention
  - Equipment calibration & qualification
  - Out of specification investigations (OOS)

# Medical Devices requirements

- Management Controls
  - Quality Policy, Quality Manual
  - Management Representative
  - Internal Audits
  - Management Review
  - Product Master Records – DMR, DHR
  - Organization Responsibilities
  - QA Independence
  - Annual Review of Quality System

# Medical Devices reqmts (cont'd)

- Building & Facility
  - Maintenance & Chemicals
  - Waste & Environmental Controls
  - Pest Control, Lighting, Water, Washrooms
- Purchasing
  - Specifications (w/ microbiological criteria)
  - Supplier audits & notification of changes
  - Qualification of consultants, subcontractors
  - Nonconforming material – ID, segregation
  - Identification, packaging & storage

# Medical Devices reqmts (cont'd)

- Design Control
  - Verification & Validation
  - Risk Analysis
  - Design Reviews & documentation
- Recalls/Corrections/Removals
  - Procedure
  - Mock Recall
  - Reporting to FDA

# Medical Devices reqmts (cont'd)

- Document Control
  - Creation & Change Control
  - SOPs & Production Processes
  - Batch Records
- Personnel & Training
  - Sanitation & Hygiene
  - Job Descriptions
  - GMP & Job-specific Training
  - Training Records

# Medical Devices reqmts (cont'd)

- Device Identification/Traceability
  - At all stages through installation - status, too
  - Device identification
  - Tracking file
- Corrective/Preventive Actions
  - SOPs, CARs & PARs
  - Nonconforming materials controls
  - Failure investigation
  - Root cause analysis

# Medical Devices reqmts (cont'd)

- Device Master Record (DMR)
  - Specifications, formulations, drawings, etc.
  - Equipment installation & maintenance
  - Calibration of QA devices used
- Device History Record (DHR)
  - For each production lot
  - Date, # units, labeling
  - Acceptance testing
  - Product Release approval

# Medical Devices reqmts (cont'd)

- Deaths, Adverse Events, Malfunctions & Complaints
  - Written procedure for management of event
  - Investigation & resolution
  - Determine need to report
- Medical Device Reporting
  - Written procedure for reporting (FDA)
  - Root cause analysis
  - Corrective actions

# Medical Devices reqmts (cont'd)

- Production & Process Controls
  - Including sterilization
  - Validation protocol – equipment, process software
  - Equipment calibration & maintenance
  - Nonconformance adjustments
- Acceptance
  - Receipt of devices
  - In-process testing
  - Release authorization (in DHR)
  - When is it “delivered??”

# Medical Devices reqmts (cont'd)

- Laboratory
  - Cleanliness
  - Waste processing
  - Methods & standards
  - Notebooks, sign-offs, tracking, preservation
  - Equipment calibration & verification
  - Reagents tested, expiry dates

# Part 11 Requirements

- Validation of computer systems
- Spreadsheet validation
- Electronic signatures procedure/training
  - FDA notification
- Record retention
- User access & change control
- Terminal locking

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