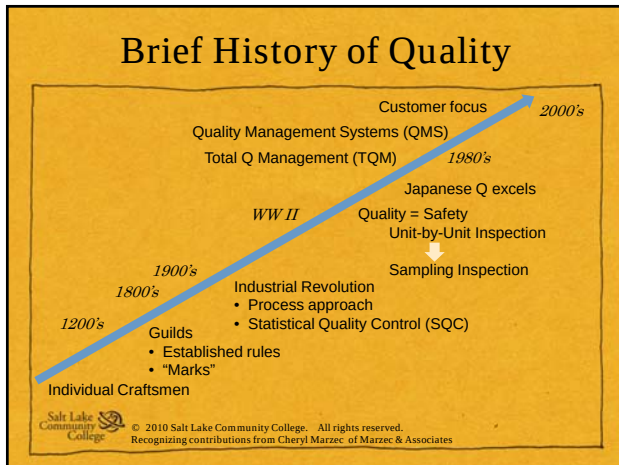
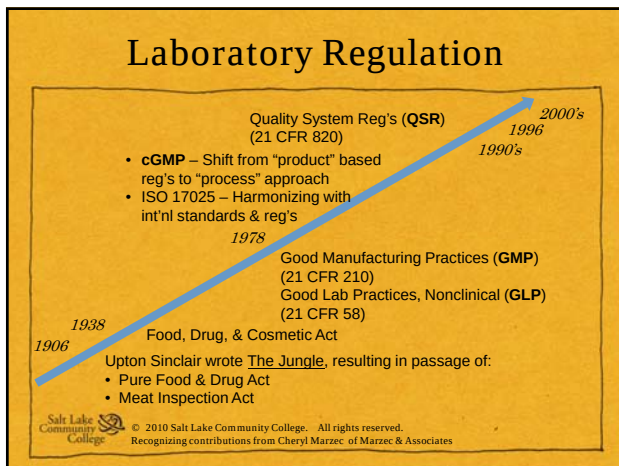
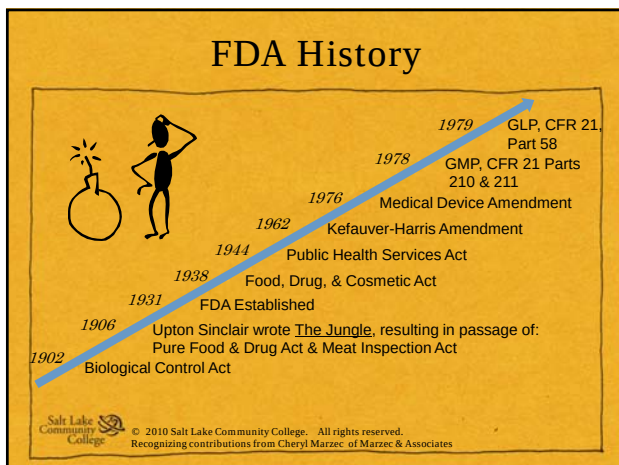
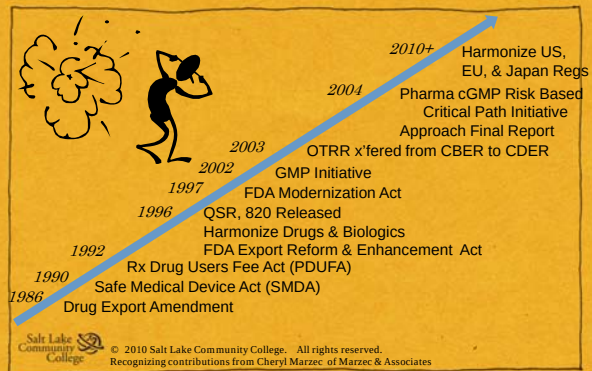








FDA More Recently



1800's

- Traveling shows sold “miracle elixirs”
- Cured all diseases know to mankind
- Try it on your animals too
- Usually had high alcohol content
- Who knows what else was added



Salt Lake Community College © 2010 Salt Lake Community College. All rights reserved. Recognizing contributions from Cheryl Marzec of Marzec & Associates

1902

- Diphtheria antitoxin in vaccine was contaminated with live tetanus bacilli
- At least 12 children died
- **Biologics Control Act** – Purity & safety of sera & vaccines required



Salt Lake Community College © 2010 Salt Lake Community College. All rights reserved. Recognizing contributions from Cheryl Marzec of Marzec & Associates

1906

- Upton Sinclair wrote The Jungle, in 1905
- Intended to be a commentary about the terrible plight of factory workers
- Unsanitary conditions of the meat packing plants caused a public uproar
 - Diseased animals sold
 - Poisoned rodents processed
 - Workers who fell into equipment were processed



© 2010 Salt Lake Community College. All rights reserved.
Recognizing contributions from Cheryl Marzec of Marzec & Associates

1906 (cont.)

- **The Public Was Outraged!**
- **Pure Food & Drug Act** – Became law
 - Illegal to sell contaminated (adulterated) meat or food
 - Illegal to put false/inaccurate info on labels
 - Dangerous ingredients (alcohol, opium, or morphine) must be listed on the label
- Gov could remove a drug from market if *adulterated or mislabeled*



© 2010 Salt Lake Community College. All rights reserved.
Recognizing contributions from Cheryl Marzec of Marzec & Associates

1931

- FDA formally established, but its roots go back much further
- Part of Executive Branch of Government



© 2010 Salt Lake Community College. All rights reserved.
Recognizing contributions from Cheryl Marzec of Marzec & Associates

1938



- **107 people, mostly children**, die after using “elixir of sulfanilamide”
 - Used to treat streptococcal infections
 - S. E. Massengil Co chemist mixed powdered form with diethylene glycol (antifreeze) to form a elixir
 - President prosecuted for **mislabeling** only
- **Food Drug & Cosmetic Act** – Requires drugs, devices, veterinary drugs, food, & cosmetics to be proven **safe**



© 2010 Salt Lake Community College. All rights reserved.
Recognizing contributions from Cheryl Marzec of Marzec & Associates

1940's

- Nearly 300 people died in 1941, after taking one company's sulfathiazole tablet
- Tainted with sedative, Phenobarbital sulfa
- FDA revised manufacturing & quality control requirements
- Beginnings of what would become **GMP's**



© 2010 Salt Lake Community College. All rights reserved.
Recognizing contributions from Cheryl Marzec of Marzec & Associates

1942

- **Public Health Service Act**
- Given authority for biologics
- Biologics must be produced in *licensed* facility
- Label required to include facility & product info
- License can be *suspended* or *revoked* if required standards not met



© 2010 Salt Lake Community College. All rights reserved.
Recognizing contributions from Cheryl Marzec of Marzec & Associates

1960's

- Thalidomide marketed in Europe as sleeping pill & morning sickness treatment
- Caused serious deformities in developing fetuses when taken by mothers in first trimester
- 10,000 severely deformed children born
- FDA reviewer denied approval of drug for use in US



© 2010 Salt Lake Community College. All rights reserved.
Recognizing contributions from Cheryl Marzec of Marzec & Associates

1962 Kefauver-Harris Amendment

- Manufacturer must prove a drug is **effective** in treating the prescribed indication, as well as being **safe**
 - Regulated clinical trial process
 - Animal testing before humans
- 1963 – First GMP for pharmaceuticals

What a concept!



© 2010 Salt Lake Community College. All rights reserved.
Recognizing contributions from Cheryl Marzec of Marzec & Associates

1976 Medical Device Amendment

- Added to the FD&C Act
- Ensured the safety & effectiveness of medical devices
- Introduces concepts of:
 - Premarket notifications & approvals
 - Performance standards



© 2010 Salt Lake Community College. All rights reserved.
Recognizing contributions from Cheryl Marzec of Marzec & Associates

1978 current Good Manufacturing Practices

- Code of Federal Regulations (CFR) 21, Parts 210-211
- Shift from “product” based reg’s to “process” approach
- *Written procedures* must be followed in manufacturing of pharmaceuticals
- Non-compliance is a **criminal act**



© 2010 Salt Lake Community College. All rights reserved.
Recognizing contributions from Cheryl Marzec of Marzec & Associates

1979 Good Laboratory Practices

- Code of Federal Regulations (CFR) 21, Parts 58
- Applies to all non-clinical studies (animal studies) of a drug or biologic
- Covers the org, personnel, protocols, lab data recording, & design of lab equipment



© 2010 Salt Lake Community College. All rights reserved.
Recognizing contributions from Cheryl Marzec of Marzec & Associates

1980's

- 12-year-old girl was given Extra strength Tylenol for a cold
- Within a few hours she died
- Six other people died too
- Johnson & Johnson did nationwide recall
- Investigation showed criminal tampering of Tylenol bottles
- Culprit has never been found



© 2010 Salt Lake Community College. All rights reserved.
Recognizing contributions from Cheryl Marzec of Marzec & Associates

1983

- Congress passed Federal Anti-Tampering act
- FDA issued tamper-resistant packaging regulations for OTC human drugs
- Regulations added to the GMPs



© 2010 Salt Lake Community College. All rights reserved.
Recognizing contributions from Cheryl Marzec of Marzec & Associates

1986 Drug Export Amendment

- Added to the FD&C Act
- Prohibits shipping of drugs that are not FDA approved to other countries



© 2010 Salt Lake Community College. All rights reserved.
Recognizing contributions from Cheryl Marzec of Marzec & Associates

1990



- **Safe Medical Device Act**
- Established new standards for devices that could cause/contribute to death, serious illness, or injury to patients



© 2010 Salt Lake Community College. All rights reserved.
Recognizing contributions from Cheryl Marzec of Marzec & Associates

1990's

- Executives for Par Pharmaceuticals bribed FDA reviewers
- Generic drugs were not tested
- Test results for the name brand drugs were accepted
- Analysts destroyed records, changed procedures, & falsified records
- All involved were debarred from the industry



© 2010 Salt Lake Community College. All rights reserved.
Recognizing contributions from Cheryl Marzec of Marzec & Associates

1992



- **Generic Drug Enforcement Act** passed by Congress
- Imposed debarment & other penalties for illegal involving abbreviated drug applications



© 2010 Salt Lake Community College. All rights reserved.
Recognizing contributions from Cheryl Marzec of Marzec & Associates

1992

- **Prescription Drug User Fee Act**
- Source of funding for FDA
- Pharmaceutical manufacturers charged a fee for each drug submitted for review
- Reduced review time from 27 to 12 months



© 2010 Salt Lake Community College. All rights reserved.
Recognizing contributions from Cheryl Marzec of Marzec & Associates

1996

- Harmonize drugs & biologics
- Eliminates requirement for firm to have additional establishment license applications for “well established drugs & biologics”
- Drugs & biologics combined on single license application



Salt Lake
Community
College

© 2010 Salt Lake Community College. All rights reserved.
Recognizing contributions from Cheryl Marzec of Marzec & Associates

1996 FDA Export Reform & Enhancement Act

- Medical devices not legally marketed in the US, could be exported if a series of requirements is met:
 - Approval in one of 24 “Tier 1” countries
 - Country must have well-developed product clearance systems
 - Tier 1 countries include Australia, Canada, Israel, Japan, and the EU



Salt Lake
Community
College

© 2010 Salt Lake Community College. All rights reserved.
Recognizing contributions from Cheryl Marzec of Marzec & Associates

1997 FDA Modernization Act

- FDA Modernization Act
- Established a framework for premarket review
- Fine tunes FDA authority including:
 - Oversight of device tracking
 - Reporting
 - PMAs & 510(k)s
- FDA required to:
 - Institute new approaches to labeling claims & intended uses
 - Identify recognized standards



Salt Lake
Community
College

© 2010 Salt Lake Community College. All rights reserved.
Recognizing contributions from Cheryl Marzec of Marzec & Associates

2002



- **GMP Initiative**
- Scope & application of CFR Part 11 (electronic documents) revisited
- Procedure for disputing inspection observations drafted
- Aseptic processing guide revised
- Inclusion of CMC reviewer on inspection teams encouraged



© 2010 Salt Lake Community College. All rights reserved.
Recognizing contributions from Cheryl Marzec of Marzec & Associates

2003

- **Office of Therapeutics Research & Review (OTRR)** transferred from Center for Biologics Evaluation & Research (CBER) to Center for Drug Evaluation & Research (CDER)
- Review of biopharmaceuticals consolidated into the Offices of Biotechnology Products (OBP) & Drug Evaluation IV (ODE IV)



Enough abbreviations?



© 2010 Salt Lake Community College. All rights reserved.
Recognizing contributions from Cheryl Marzec of Marzec & Associates

2004

- **Critical Path Initiative**
- New product development toolkit improves efficiency & predictability of development process from lab conception to commercial product
- Areas ID'ed for improvement & streamlining: assessing safety, demonstrating medical utility & industrialization



© 2010 Salt Lake Community College. All rights reserved.
Recognizing contributions from Cheryl Marzec of Marzec & Associates

2004

- Pharmaceutical cGMP in 21st century
- Risk management based approach to pharmaceutical manufacturing
- New framework for regulatory oversight of quality system



© 2010 Salt Lake Community College. All rights reserved.
Recognizing contributions from Cheryl Marzec of Marzec & Associates

2004 (cont.)

- Applications for new pharmaceuticals & biotech directed to one of four centers for review:
 - Center for Drug Evaluation & Research (CDER)
 - Center for Biologics Evaluation & Research (CBER)
 - Center for Devices & Radiologic Evaluation (CDRE)
 - Center for Veterinary Medicine (CVM)
- Mission: Protection the health of the public



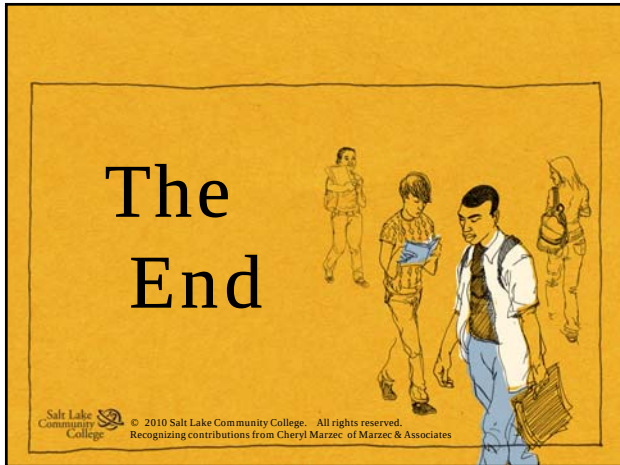
© 2010 Salt Lake Community College. All rights reserved.
Recognizing contributions from Cheryl Marzec of Marzec & Associates

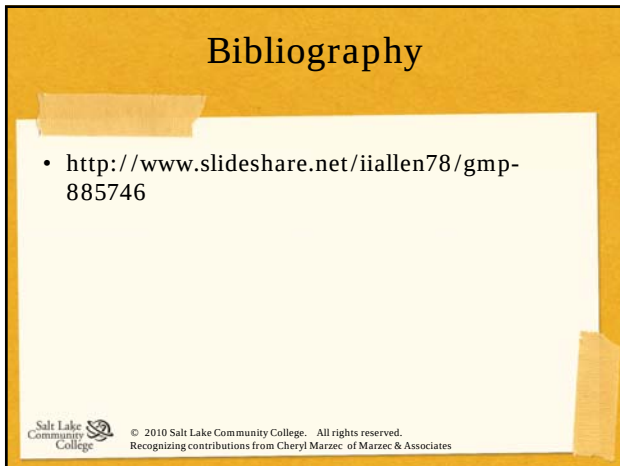
2010+

- Future of Standards & Reg's
- Product acceptance of drugs, devices, & biologics between US, EU, & Japan
- Common standard requirements or common standards between US, EU, & Japan
- ICH documents being released

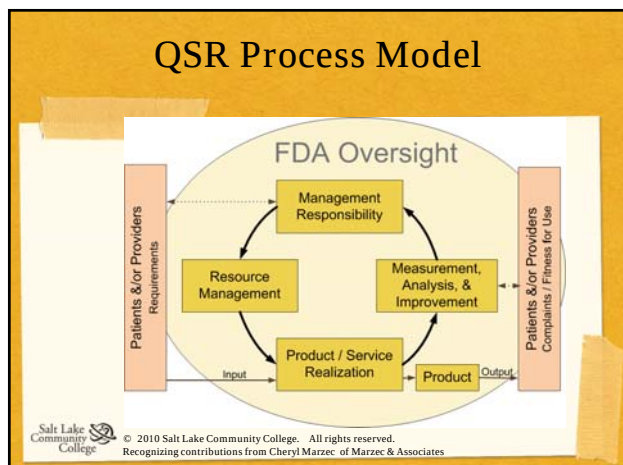


© 2010 Salt Lake Community College. All rights reserved.
Recognizing contributions from Cheryl Marzec of Marzec & Associates





QSR Process Model



§820.180 – General Requirements

- Records must be accessible to the manufacturer & FDA inspectors & legible
- Computerized records must be backed up
- Confidential records must be marked
- Records must be retained for the expected life of the device or at least two years
- Some records are exempted



Salt Lake Community College logo and copyright information: © 2010 Salt Lake Community College. All rights reserved. Recognizing contributions from Cheryl Marzec of Marzec & Associates.

Subpart D, § 820.40 – Document Controls

Procedures for controlling documents includes:

- Review & approval by designated people prior to issue
- Documents available at points of use
- Obsolete documents removed from use
- Changes reviewed & approved, date of effectivity included
- Changes described & communicated appropriately



Salt Lake Community College logo and copyright information: © 2010 Salt Lake Community College. All rights reserved. Recognizing contributions from Cheryl Marzec of Marzec & Associates.

Subpart M, Records

Records required:

§820.180 – General Requirements

§820.181 – Device Master Record

§820.184 – Device History Record

§820.186 – Quality System Record

§820.198 – Complaint Files



© 2010 Salt Lake Community College. All rights reserved.
Recognizing contributions from Cheryl Marzec of Marzec & Associates

§820.181 – Device Master Record

Contains info needed to mfg. the product

- Device specs (drawing, formulations, S/W specs)
- Production process specs (equip specs & production methods, procedures, & enviro specs)
- Installation, servicing, & maintenance procedures & methods
- QA procedures, specs, & QA equip used
- Packaging & labeling specs



Included in the DMR for each device type



© 2010 Salt Lake Community College. All rights reserved.
Recognizing contributions from Cheryl Marzec of Marzec & Associates

§820.184 – Device History Record

Contains info on each batch or unit mfg'ed

- Manufacturing dates
- Quantity manufactured
- Quantity released for distribution
- Acceptance records showing device manufactured according to DMR
- Label & labeling used for each production unit
- Device ID & control numbers



Included in DHR for each batch or unit



© 2010 Salt Lake Community College. All rights reserved.
Recognizing contributions from Cheryl Marzec of Marzec & Associates

§820.186 – Quality System Record

- File contains procedures & other required activities that are not specific to type of device
- Includes any documents required by §820.20 Management Responsibility section



© 2010 Salt Lake Community College. All rights reserved.
Recognizing contributions from Cheryl Marzec of Marzec & Associates

§820.198 – Complaint Files

- Procedure required for receiving, reviewing, & evaluating all complaints
 - Complaints are uniformly & promptly processed
 - Oral complaints are documented
 - Complaints are reported to FDA, if required
- Complaints evaluated to see if investigation is required
- Device not meeting spec must be reviewed, evaluated, & investigated



© 2010 Salt Lake Community College. All rights reserved.
Recognizing contributions from Cheryl Marzec of Marzec & Associates

§820.180 – Complaint Files (cont.)

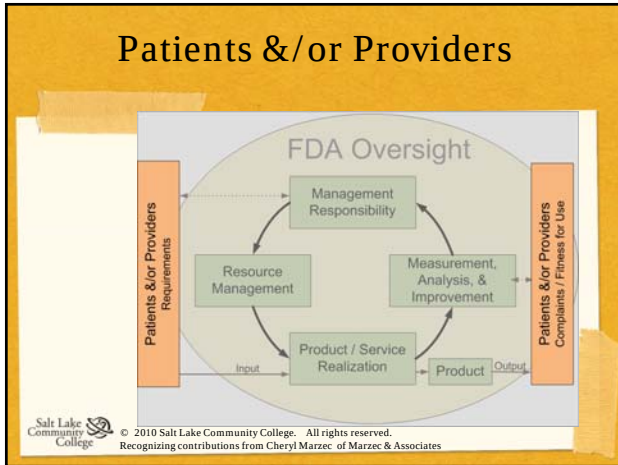
Any event reported to FDA UNDER 803 or 804, must be kept in a separate file & include:

- Whether device failed to meet specs
- Was device used for treatment or diagnosis
- Relationship of device to reported incident
- Other investigative info

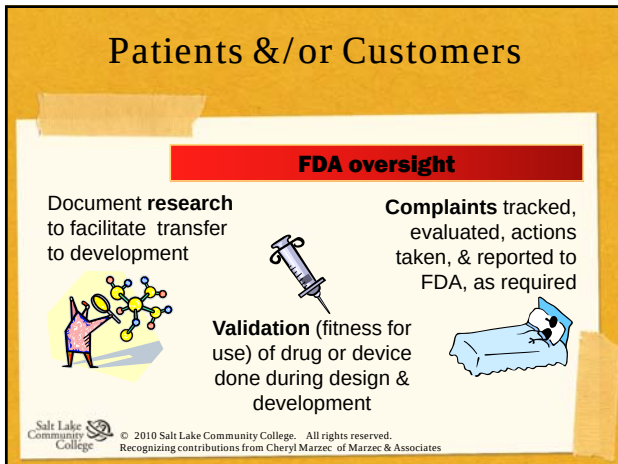


© 2010 Salt Lake Community College. All rights reserved.
Recognizing contributions from Cheryl Marzec of Marzec & Associates

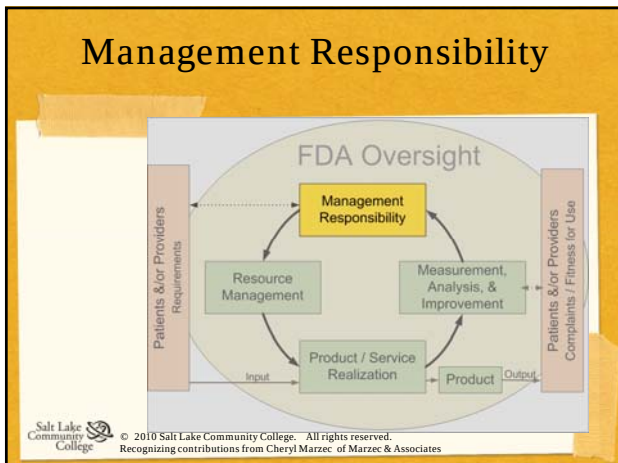
Patients &/or Providers



Patients &/or Customers



Management Responsibility



Management Responsibility

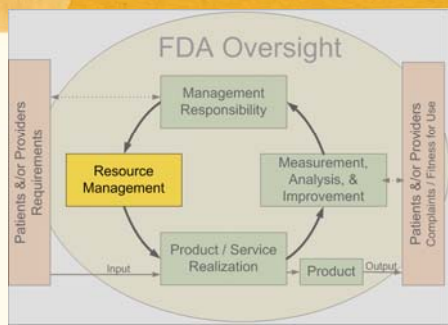
Subpart B, § 820.20

- Establish quality policy
- Establish organizational structure
 - Determine responsibility & authority
 - Provide resources
 - Appoint management representative
- Hold QSR reviews
- Plan for quality
- Develop quality system procedures & instructions



© 2010 Salt Lake Community College. All rights reserved.
Recognizing contributions from Cheryl Marzec of Marzec & Associates

Resource Management



© 2010 Salt Lake Community College. All rights reserved.
Recognizing contributions from Cheryl Marzec of Marzec & Associates

Resource Management Subpart B, §820.25 – Personnel

- Personnel must have necessary education, background, training, & experience
- Procedures are needed to identify training needs & ensure training is adequate and documented
 - Personnel are made aware of potential device defects
 - Verification & validation personnel are made aware of potential defects & errors



© 2010 Salt Lake Community College. All rights reserved.
Recognizing contributions from Cheryl Marzec of Marzec & Associates

Resource Management Subpart B, §820.25 – Personnel (Cont.)

- In the QMS, these areas are addressed under Resource Management
 - Environmental controls
 - Personnel
 - Buildings
- In the QSR, they are addressed under Subpart G, §820.70 – Production & Process Controls



© 2010 Salt Lake Community College. All rights reserved.
Recognizing contributions from Cheryl Marzec of Marzec & Associates

Product / Service Realization



© 2010 Salt Lake Community College. All rights reserved.
Recognizing contributions from Cheryl Marzec of Marzec & Associates

Production Flow

Research

↓
Design & Develop

↓
Manufacture Product

↓
Inspect & Test

↓
Deliver Product or
Service to Patient
or Provider



© 2010 Salt Lake Community College. All rights reserved.
Recognizing contributions from Cheryl Marzec of Marzec & Associates

Research to D & D

Plan ahead!

Prepare documents & maintain records as you do your research



Research

May or may not result in a product



Design & Development

Results in a product



© 2010 Salt Lake Community College. All rights reserved.
Recognizing contributions from Cheryl Marzec of Marzec & Associates

D & D



Planning
(User Needs)

Review &
Approval

Design Inputs

File outputs in
•DMF
•DHR

Verification

Design Outputs

Validation

Product



© 2010 Salt Lake Community College. All rights reserved.
Recognizing contributions from Cheryl Marzec of Marzec & Associates

Subpart C, §820.30 – Design Controls

Design & Development
Planning

Requirements
Specification

Cheryl
1-3-2010

Inputs

Requirements
Inspection &
Test Plans

Bob
1-3-2010

Outputs

Validation
Results

Linda
1-3-2010

Verification
Inspection &
Test Reports

Elmer
1-3-2010

Design History File

Records showing
design developed
as per plan & req's

Design Transfer

Production Specs

Design Changes
Controlled Throughout



© 2010 Salt Lake Community College. All rights reserved.
Recognizing contributions from Cheryl Marzec of Marzec & Associates

Subpart E, §820.50 – Purchasing Controls

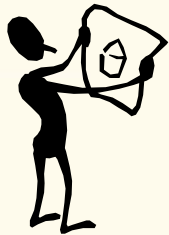
Procedures to ensure received product & services conform to requirements

- Evaluate and document suppliers, contractors, and consultants
- Identify appropriate controls
- Maintain record of acceptability
- Describe requirements fully, including quality requirements, in Purchasing Data
- Ensure supplier notifies org of any changes so org can evaluate



© 2010 Salt Lake Community College. All rights reserved.
Recognizing contributions from Cheryl Marzec of Marzec & Associates

Subpart F, §820.60 – Identification



Procedures required to identify product at:

- Receipt
- Production
- Distribution
- Installation



© 2010 Salt Lake Community College. All rights reserved.
Recognizing contributions from Cheryl Marzec of Marzec & Associates

Subpart F, §820.65 – Traceability

- Applies to devices intended for surgical implant or support or sustain life
- Procedures required to ID each lot, batch, or device & components with a control number
- Facilitates corrective action
- Document ID recorded in DHR



© 2010 Salt Lake Community College. All rights reserved.
Recognizing contributions from Cheryl Marzec of Marzec & Associates

Subpart G, §820.70 – Production & Process Controls

- Develop, conduct, control, & monitor production processes
- Controls include:
 - SOP's that control production
 - Compliance w/ standards & codes
 - Criteria for workmanship
 - Monitoring & control of process parameters & device characteristics
 - Approval of processes & process equipment



© 2010 Salt Lake Community College. All rights reserved.
Recognizing contributions from Cheryl Marzec of Marzec & Associates

Subpart G, §820.70 – Production & Process Controls (cont.)

- Control, verify, validate, & approve processes changes
- Control & inspect environmental conditions
- Set requirements for personnel's health, cleanliness, personal practices, & clothing
- Prevent contamination of equipment
- Maintain suitable building design & space



© 2010 Salt Lake Community College. All rights reserved.
Recognizing contributions from Cheryl Marzec of Marzec & Associates

Subpart G, §820.70 – Production & Process Controls (cont.)

- Remove or limit manufacturing materials that could have an adverse effect on quality & document
- Validate computer software that is used in production or quality system before use & document



© 2010 Salt Lake Community College. All rights reserved.
Recognizing contributions from Cheryl Marzec of Marzec & Associates

Subpart G, §820.70 – Production & Process Controls (cont.)

Ensure manufacturing equipment meets req's, is appropriate for use & maintained

- Schedule, perform, & document maintenance
- Inspect equipment periodically & document inspection
- Limits & tolerances of equipment requiring periodic adjustment are posted or available



© 2010 Salt Lake Community College. All rights reserved.
Recognizing contributions from Cheryl Marzec of Marzec & Associates

Subpart G, §820.72 – Inspection, Measurement, & Test Equipment

- Procedures required to ensure IM&TE is:
 - Suitable for its intended use
 - Calibrated, inspected, checked, & maintained
 - Accuracy & fitness for use maintained
- When documented calibration instructions are not met, effect on quality is evaluated
- Calibration standards traceable to national or international standards
- Mark equipment & maintain records



© 2010 Salt Lake Community College. All rights reserved.
Recognizing contributions from Cheryl Marzec of Marzec & Associates

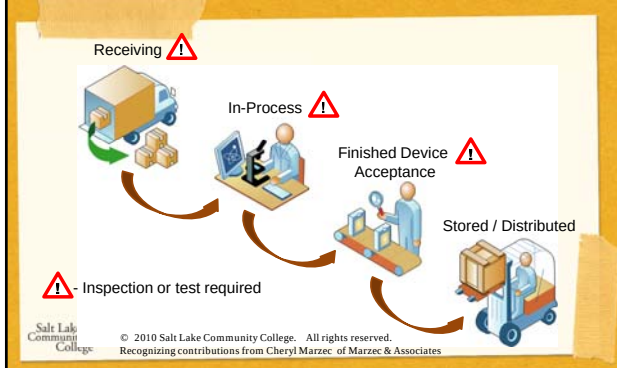
Subpart G, §820.75 – Process Validation

- Applies when results of process can't be verified by inspection & test; process must be validated
- Procedures for controlling process parameters must be monitored & controlled to ensure they're met
- Changes or deviations must be reviewed & revalidated if necessary



© 2010 Salt Lake Community College. All rights reserved.
Recognizing contributions from Cheryl Marzec of Marzec & Associates

Subpart H, §820.80 – Acceptance Activities



Subpart H, §820.80 – Acceptance Activities

- Procedures required for all production phases to ensure requirements are met
- Finished devices are quarantined until DMR requirements completed
- Records are part of DHR
- Conforming / nonconforming status must be indicated
- Product not used unless acceptance activities are passed

The Salt Lake Community College logo and copyright information are at the bottom.

Subpart I, §820.90 – Nonconforming Product

- Product not conforming to req's must be identified, documentation, evaluated, segregated, & disposed of appropriately
- Evaluation includes determining if additional investigation is needed
- Review, rework, & disposition of nonconforming product are documented
- Reworked product is reevaluated before release & documented in DHR

The Salt Lake Community College logo and copyright information are at the bottom.

Subpart K – Labeling & Packaging Control

§820.120 Device Labeling

Procedures required to control labeling activities



- Printed labels must remain legible & affixed
- Labeling not released until checked for accuracy; release recorded in DHR
- Labels stored & used in operations are managed so they can be identified & not mixed up
- Labels used for each unit/batch are recorded in DHR

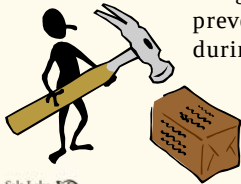


© 2010 Salt Lake Community College. All rights reserved.
Recognizing contributions from Cheryl Marzec of Marzec & Associates

Subpart K – Labeling & Packaging Control

§820.130 Device Packaging

Packaging & shipping containers designed & constructed to prevent alteration or damage during all phases



© 2010 Salt Lake Community College. All rights reserved.
Recognizing contributions from Cheryl Marzec of Marzec & Associates

Subpart L – Handling, Storage, Distribution & Installation

§820.140 Handling

Procedures are required to ensure mix ups, damage, deterioration, contamination, etc. don't occur during handling



© 2010 Salt Lake Community College. All rights reserved.
Recognizing contributions from Cheryl Marzec of Marzec & Associates

Subpart L – Handling, Storage, Distribution & Installation

§820.150 Storage

- Procedures required for storage areas & stock rooms to ensure mix ups, damage, deterioration, contamination, etc. don't occur
- Product deteriorating over time must be rotated & condition assessed as appropriate
- Procedures for authorizing receipt from & dispatch to storage or stock are required



© 2010 Salt Lake Community College. All rights reserved.
Recognizing contributions from Cheryl Marzec of Marzec & Associates

Subpart L – Handling, Storage, Distribution & Installation

§820.160 Installation

- If installation is required, instructions must be available
- Instructions must be distributed with the device or available to the installer
- Installer must ensure installation, inspection, & any testing are performed & documented



© 2010 Salt Lake Community College. All rights reserved.
Recognizing contributions from Cheryl Marzec of Marzec & Associates

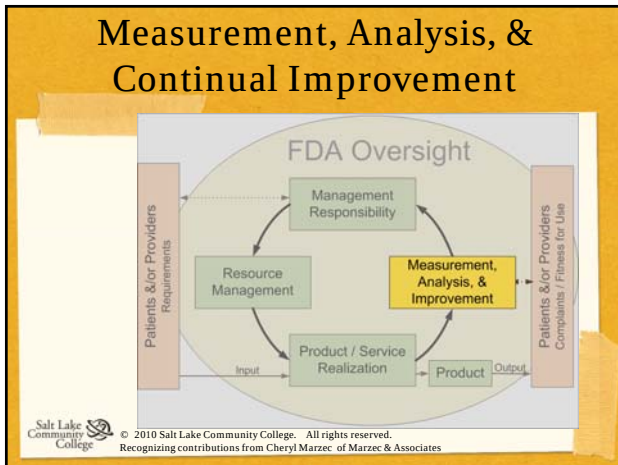
Subpart N, §820.200 – Servicing

- If servicing is required, instructions & procedures must be maintained for performing & verifying that service is done according to requirements
- Service reports must be documented completely
- Service reports must be analyzed for corrective actions, reported to FDA, if required, & handled as a complaint if there are deviations
- Reports must be documented



© 2010 Salt Lake Community College. All rights reserved.
Recognizing contributions from Cheryl Marzec of Marzec & Associates

Measurement, Analysis, & Continual Improvement



§ 820.22 – Quality Audit

- Often called inspections or assessments
- Audits are conducted according to procedure to ensure:
 - Org's quality system complies with requirements of QSR
 - Org's quality system is effective
- Corrective action required
- Results of audits & reaudits documented



© 2010 Salt Lake Community College. All rights reserved.
Recognizing contributions from Cheryl Marzec of Marzec & Associates

Subpart J, §820.100 – Corrective & Preventive Action

Procedures required for performing corrective & preventive action



- Analyze source of problem or potential problem
- Investigate the cause
- Identify actions needed to correct & prevent reoccurrence
- Verify or validate effectivity of actions take
- Implement & record changes
- Disseminate information & submit for mgt. review

© 2010 Salt Lake Community College. All rights reserved.
Recognizing contributions from Cheryl Marzec of Marzec & Associates

Subpart O, §820.250 – Statistical Techniques

- Where appropriate, procedures are required for identifying statistical techniques to ensure acceptable process capability & product characteristics
- Sampling plans must be rational
- Sampling methods must be appropriate & reviewed when changes occur
- If it isn't documented, it didn't happen



© 2010 Salt Lake Community College. All rights reserved.
Recognizing contributions from Cheryl Marzec of Marzec & Associates

The End



© 2010 Salt Lake Community College. All rights reserved.
Recognizing contributions from Cheryl Marzec of Marzec & Associates
