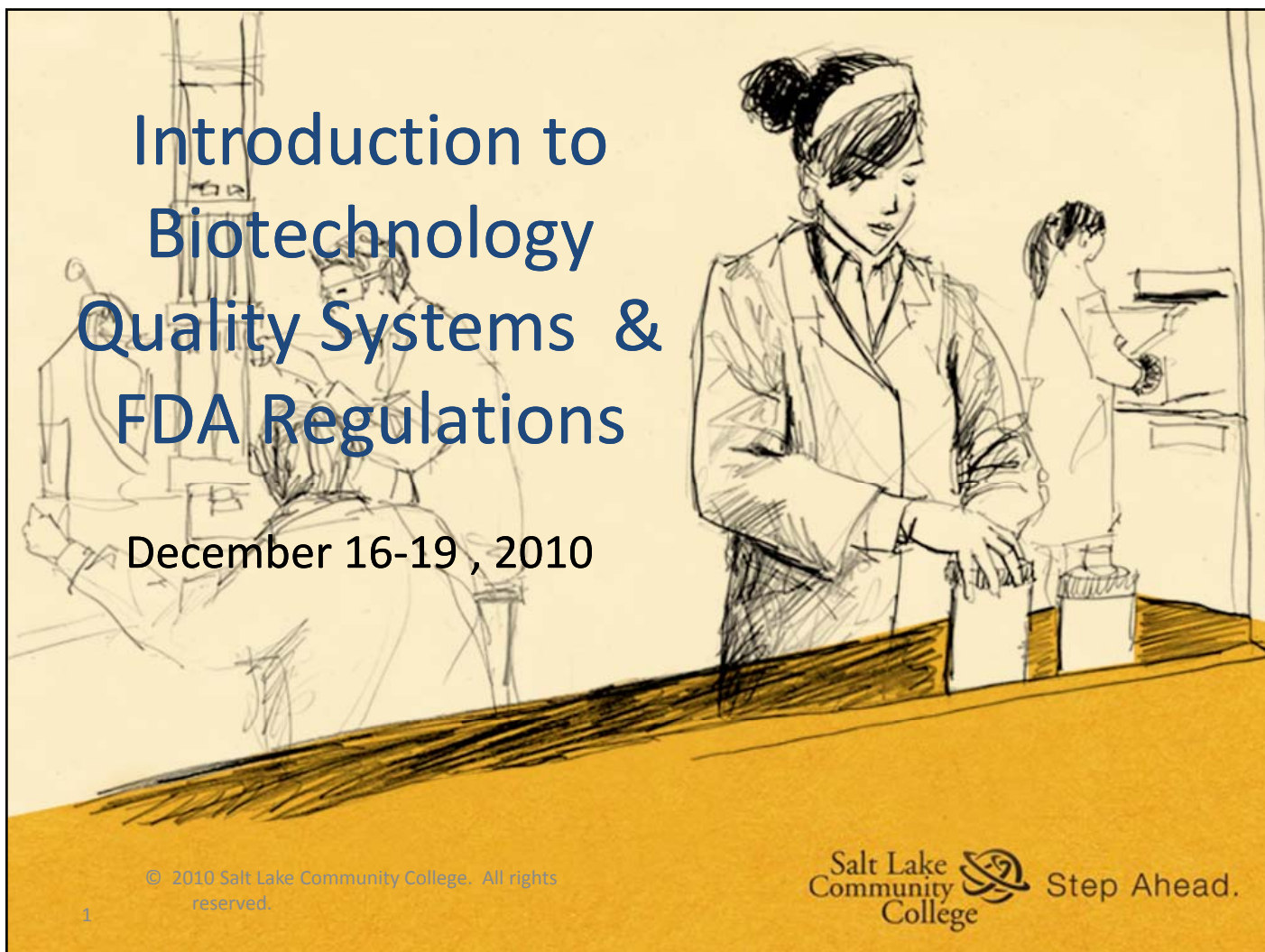


Introduction to Biotechnology Quality Systems & FDA Regulations

December 16-19 , 2010



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DAY 1

THURSDAY, DECEMBER 16

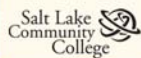


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INTRODUCTIONS

- Name
- Institution
- Position
- Education / work history
- Biotech industry experience?
 - If yes, then how many years, and what did you do?
- Expectations from this workshop

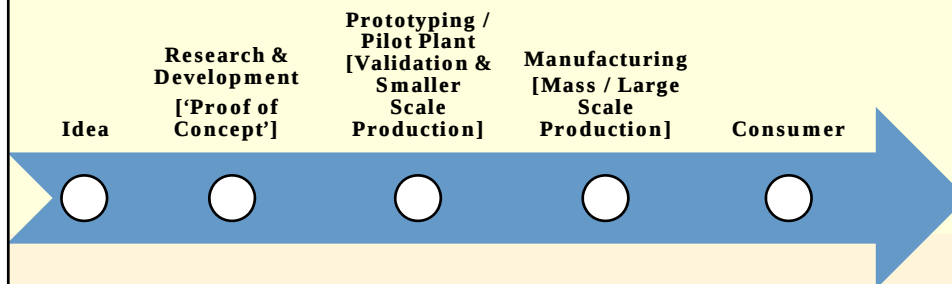


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BIOTECHNOLOGY INDUSTRY OVERVIEW

BIOTECHNOLOGY INDUSTRY



RESEARCH & DEVELOPMENT



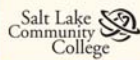
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GOALS

- Transformation : idea → marketable product
- Research (scientific & market) = to figure out what the product will be (customer requirements ; design specifications)
- Development = design and optimize “final product”

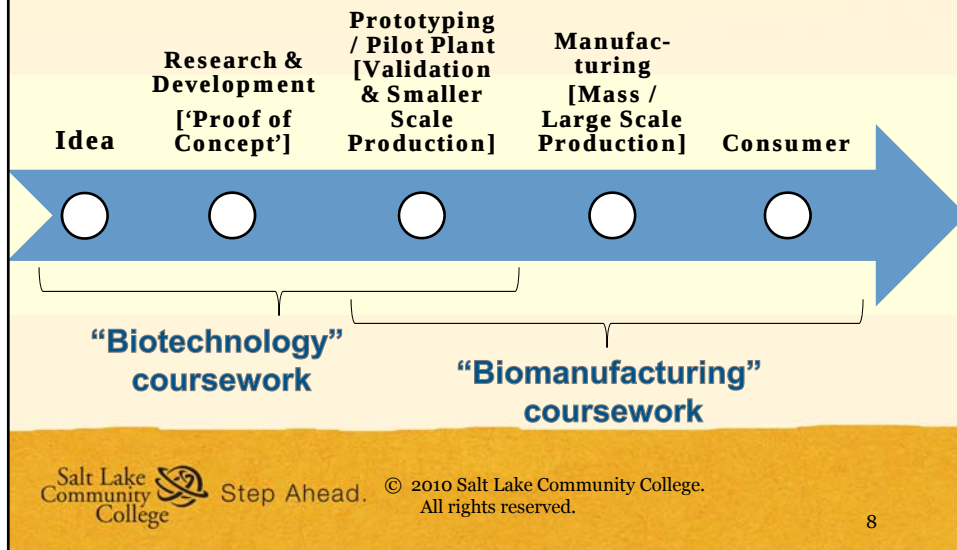
*** Strategic !



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BIOTECHNOLOGY INDUSTRY



MANUFACTURING

TRANSFER CONSIDERATIONS

- Prototyping / Pilot Plant phase : product transfers from R&D to production
- Scale up issues must be resolved during transfer phase
- Biomanufacturing can begin during this transfer phase
- Manufacturability must be designed into product – otherwise it will cost \$\$\$

PHASES

- Production planning
- Raw material acquisition
- Production run
- Assembly
- Packaging and labeling
- Inspection and release
- Distribution and customer support
- Continuous improvement

PRODUCTION PLANNING

- Identify **resources** required
 - ✓ Materials
 - ✓ People
 - ✓ Equipment & tools
 - ✓ Facilities
 - ✓ Time
 - ✓ \$\$\$
- Identify **processes** required
 - o Process = any operation or technique used to transform materials into products
 - o Involves technology : engineering and science considerations

RAW MATERIAL ACQUISITION

- Identify source(s)
- Qualify vendor
 - o Regulatory requirement
- Purchase raw materials
- Inspect incoming raw materials
 - o Released for use if meet specifications
 - o Quarantined / rejected if not
- Add to inventory: traceability!

PRODUCTION RUN

- Verify all raw material availability
- Schedule production run
- Perform line clearance before starting
- Follow appropriate work instructions
 - ✓ Approved
 - ✓ Most current
- Manage resources throughout

PRODUCTION RUN (cont.)

- Product must meet desired specifications /requirements
- Monitor / control production to ensure quality
- Complete batch record with production run
- Typically, entire run = one “LOT” or “BATCH”
- Deviations? Get approval & document

ASSEMBLY

- Some products are made from smaller parts/subassemblies
 - ☐ May be made in-house or by a supplier/vendor
 - ☐ Finished product company has bears overall responsibility over parts/subassemblies used – importance of vendor qualification
- Subassemblies can be made
 - ☐ Prior to final product – “stocked”
 - ☐ Just in time for use in final product
- Traceability is critical !!

PACKAGING AND LABELLING

- Package product appropriately
 - ☐ Maximize product stability and integrity
 - ☐ Sterility concerns?
- Label product appropriately (labels & product inserts)
 - ☐ Must follow federal regulations
 - ☐ All claims must have supporting data

INSPECTION AND RELEASE

- Finished product inspected to ensure quality and consistency
 - ❑ Various levels of visual checks – cross-referenced with documentation
 - ❑ May include testing: sampling vs. 100% testing
 - ❑ Verify product meets desired specifications / requirements

DISTRIBUTION AND CUSTOMER SUPPORT

- Sales and marketing – can tie in to R&D
- Warehousing
- Shipping
- Customer service / technical support

CONTINUOUS IMPROVEMENT

- Can always improve on any and all phases :
 - ☐ Resource scheduling
 - Shifts
 - Equipment maintenance
 - ☐ Production
 - Supply chain management
 - Inventory: transit, material, work-in-progress, buffer, finished goods
 - Lean manufacturing
 - Just-in-time manufacturing
 - ☐ Quality assurance

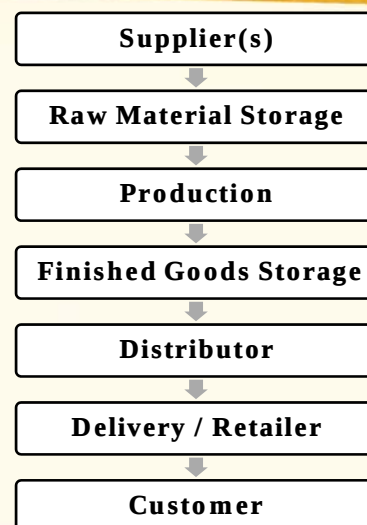
PRODUCTION CONSIDERATIONS

TIME COSTS \$\$\$

- Time includes
 - Supplier lead times
 - Equipment set-up
 - Scheduled maintenance
 - Production
 - Unexpected events: breakdowns/repairs, delivery delays
- Minimizing downtime → minimizes costs
 - Preventative maintenance vs. repairs (aka corrective maintenance)
 - Maximize use of production equipment
 - Maximize quality

SUPPLY CHAIN

- Supply chain management = coordination of supply chain elements to maximize efficiency and profit
- Effective management results in:
 - ✓ Shorter lead times
 - ✓ Reduced inventory costs
 - ✓ Faster response to demand changes



WORK FLOW & FACILITIES

- Work flow is impacted by facility layout
 - ❑ Typical layouts: product vs. process
 - ❑ Cellular layout: newer, lean philosophy
 - Work cell = combination of process and product layout
 - Flexible, so amenable to customization as needed
 - Typically 3-12 workers per cell, CROSS-TRAINED !
 - Cell is responsible for all aspects of product – output & quality
 - ❑ Line balancing: assignment of tasks at a station/cell to maximize efficient output

PRODUCTION SYSTEMS

Characteristic	Push System	Pull System
Production trigger	Forecasted demand	Customer demand
Buffer and WIP inventory size	Large	Small
Production run length	Long	Short
Product changeover speed	Slow	Fast
Effect of supply disruption	Can continue until WIP inventory is exhausted	Stops until supply is replenished
Speed of response to demand change	Slow	Fast
Effect of scheduled maintenance	Depends on WIP inventory	Production stops

PRODUCTION SYSTEMS (cont.)

- Adaptations of PULL system:

- ☐ Agile manufacturing:

- Uses flexible automation – minimal changes in tooling / software
 - Cross-training is critical
 - Allows rapid development of new products

- ☐ Just-In-Time (JIT) production:

- Reduces inventory and waste by balancing material flow
 - Permits temporary buffer inventory
 - Biggest risk = interruption of material flow; good supply chain management is critical (e.g. multiple suppliers)

MATERIALS INVENTORY

- Types of inventory:

- ☐ Transit
 - ☐ Raw materials / parts
 - ☐ Work-in-process (WIP)
 - ☐ Buffer = safety stock
 - ☐ Maintenance repair and operations (MRO) = machine parts & tools
 - ☐ Finished goods (FG) = final product

- Inventory costs \$\$\$: carrying costs vs. shortage costs

DOCUMENTATION

- Absolutely critical to the production process
- Types of production documents include
 - Standard operating procedures (SOPs)
 - Work instruction documents (WIDs)
 - Work orders
 - Batch records
 - Maintenance records
 - Testing records
 - Shipping records
- Written documents are most typical, but moving to electronic documentation

DOCUMENTATION (cont.)

- Purpose of documentation include:
 - ✓ Provides a reference for every action
 - ✓ Provides a reference for results of every measurement / test
 - ✓ Ensure all procedures and regulations were followed
 - ✓ Help all workers understand the process
 - ✓ Provides a means of communication between teams / groups within a company
 - ✓ Identifies opportunities for improvement
 - ✓ Provides justification for change
 - ✓ Provides a way to trace materials, especially for corrective action

QUALITY & REGULATIONS – AN ABBREVIATED HISTORY & INFLUENCES



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QUALITY EVOLUTION



GUILDS

- Developed strict rules for product & service Quality
- Flawless goods “marked” by inspectors
- Craftsman “marked” goods they made with second mark to track origin of goods
- Eventually, craftsman’s “mark” came to represent his reputation



INDUSTRIAL REVOLUTION

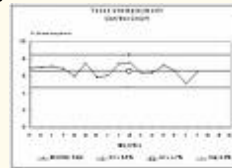
- Factory system
 - Craftsmen → factory workers
 - Shop owners → production supervisors
- Inspection of final product to weed out defective units
- Workers less empowered
- While productivity ↑ , quality ↓



WALTER SHEWHART



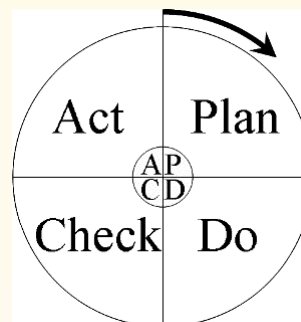
- Bell Labs statistician who helped improve reliability of buried equipment:
 - ✓ Developed concept of statistical control
 - ✓ Developed control charts
 - ✓ Differentiated *common* cause vs. *special* cause
- By eliminating *special* cause, can:
 - ✓ Predict output
 - ✓ Manage process economically



W. EDWARDS DEMING



- US Dept of Agriculture & Census Bureau statistician
- Assisted US WW II effort w/ statistical control
- Sent to Japan by USDA to aid in post-war recovery
- Major influence in Japan's transformation : "Japanese junk" → high quality products



W. EDWARDS DEMING (cont.)

Deming's version of the national anthem, which addresses people's inability to hit all the notes, serves as a metaphor for one of his points for management:

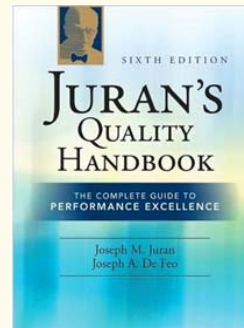
“Don't blame the singers (**workers**) if the song is written poorly (**the system is the problem**); instead, rewrite the music (**fix the system**).”

In life and in art, Deming simply wanted to make it easier for people to sing.

JOSEPH M. JURAN



- **Total quality** not just product quality
- Taught Japanese managers quality principals in 1950s
- Predicted quality of Japanese goods would overtake quality of US goods by mid-1970s
- Wrote THE book on quality
Juran's Quality Handbook



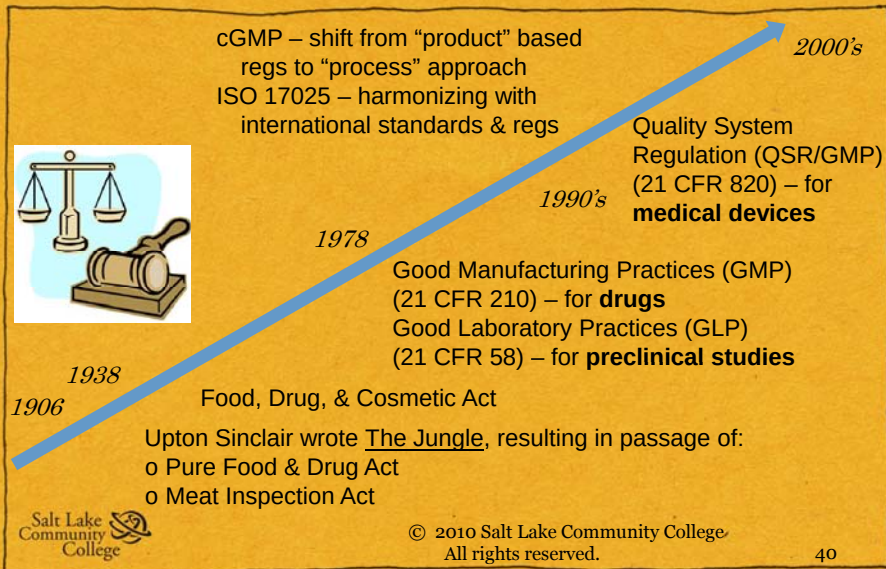
CURRENT QUALITY

- ISO 9000 standards family: describes quality management systems
- Malcolm Baldrige National Quality Award: established in 1987; managed by NIST and administered by ASQ
- Six Sigma: Motorola-developed methodology to reduce defects (≤ 3.4 defects per million)
- Quality has moved beyond manufacturing, into service, healthcare, education, and government

QUALITY REFERENCES

- “A History of Quality” : <http://asq.org/learn-about-quality/history-of-quality/overview/overview.html>
- Deming (1982) Quality, Productivity and Competitive Position
- Juran and De Feo (2010) Juran’s Quality Handbook, 6th edition
- asq.org

REGULATIONS EVOLUTION



PURE FOOD AND DRUG ACT

- Federal law enacted in 1906
- “ *for preventing the manufacture, sale, or transportation of adulterated or misbranded or poisonous or deleterious foods, drugs, medicines, and liquors, and for regulating traffic therein, and for other purposes*”
- First regulation of product labeling
- Enforced by USDA Bureau of Chemistry

FOOD, DRUG, AND COSMETIC (FD&C) ACT

- Replaced Pure Food and Drug Act
- Arose from 107 deaths related to sulfanilamide elixir in 1937: poisonous diethylene glycol used as a solvent
- Gave Food and Drug Administration (FDA) authority to oversee safety of food, drug, and cosmetics

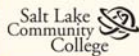
FOOD, DRUG, AND COSMETIC (FD&C) ACT (cont.)

- Includes new provisions :
 - o Requires new drugs to be shown safe before marketing
 - o Eliminates Sherley Amendment requirement to prove intent to defraud in drug misbranding cases
 - o Extends control to cosmetics and therapeutic devices
 - o Requires safe tolerances for unavoidable poisonous substances
 - o Authorizes identity, quality, and fill-of-container food standards
 - o Authorizes factory inspections
 - o Adds court injunctions to the previous penalties

ORIGIN OF THE FOOD AND DRUG ADMINISTRATION

- Mid-1860s : USDA Division of Chemistry – investigated adulteration of agricultural commodities; expanded to include food and drugs in early 1880s
- 1901 : name change – USDA Bureau of Chemistry
- 1927 : Food, Drug, and Insecticide Administration – bureau's non-regulatory research functions transferred elsewhere
- 1930 : name shortened to Food and Drug Admin.

From: www.fda.gov/AboutFDA/WhatWeDo/History/Origin/ucm124403.htm

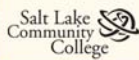


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REGULATIONS REFERENCES

- FDA : What We Do : History
<http://www.fda.gov/AboutFDA/WhatWeDo/History/default.htm>
- Sinclair (1906) The Jungle
- Deming (1982) Quality, Productivity and Competitive Position
- Juran and De Feo (2010) Juran's Quality Handbook, 6th edition



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VARIATION – IMPACTS ON QUALITY

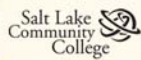


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CAUSES FOR VARIATION

- **Special** causes (accounts for 15% of variation)
 - o Unexpected / unusual occurrences not inherent in process
 - o Might be called **assignable** causes
- **Common** causes (accounts for 85% of variation)
 - o Variation is natural part of the process (operating as designed)
 - o Might be called **system** or **chance** causes



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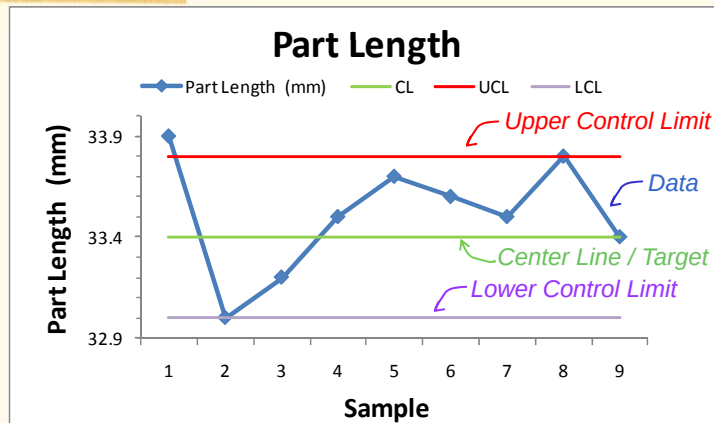
REQUIRED ACTIONS

- For **Special** causes:
 - o Investigate and identify source; correct appropriately
 - o Process modifications not necessary
- For **Common** causes:
 - o Often requires management input to change inherent feature(s) of process to make process more **reliable** (less variation)
- Resist **tampering** – making minor adjustments without understanding; may worsen variation

CONSIDERATIONS

- Key to controlling process (and hence quality) is controlling variation
- Useful tool : **statistical process control (SPC)**
 - o Method of monitoring process during operation to control quality during production rather than afterward by inspection
 - o Requires data gathering and charting
 - o Can be used to predict potential problems as well as improve process (minimize variation)

SPC CHART



PRACTICAL ACTIVITIES

To reinforce these concepts:

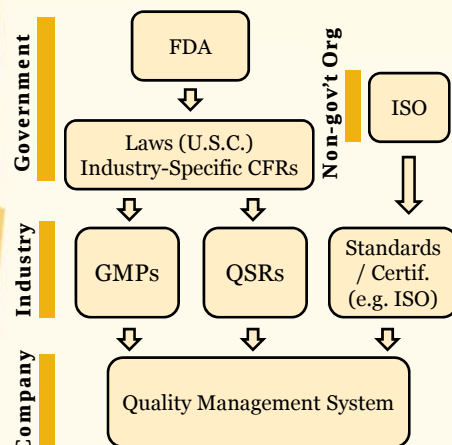
1. Control variation in a drug manufacturing process – simulation
2. Prepare statistical process control (SPC) charts – is the process in control ? why?

QUALITY & REGULATORY RELATIONSHIPS

THE HIERARCHY

A tight relationship exists between

- ☐ the FDA [regulating body]
- ☐ the Laws [US Code]
- ☐ the Code of Federal Regulations (CFRs) - gov't agency promulgated
- ☐ Good Manufacturing Practices (GMPs)
- ☐ Quality System Regulations (QSRs)
- ☐ Standards / Certifications (e.g. ISO)
- ☐ Quality Management System



COMPLYING WITH FDA REGS

How ?



SPEED LIMIT SIGN



NO LITTERING SIGN



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COMPLYING WITH FDA REGS ... 2

By appropriately
interpreting the
regulations



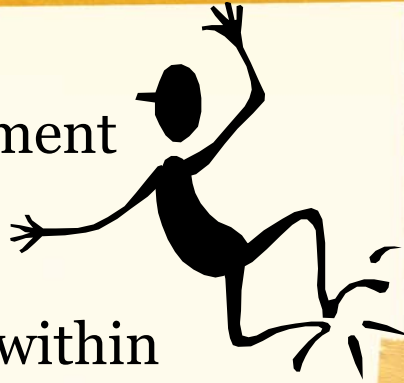
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COMPLYING WITH FDA REGS ... 3

A quality management system provides a structure for the company to work within and remain compliant



FOOD AND DRUG ADMINISTRATION

FDA OVERVIEW

- An agency of Department of Health and Human Services
- Mission:
 1. “responsible for protecting the public health by assuring the safety, efficacy, and security of human and veterinary drugs, biological products, medical devices, our nation’s food supply, cosmetics, and products that emit radiation”

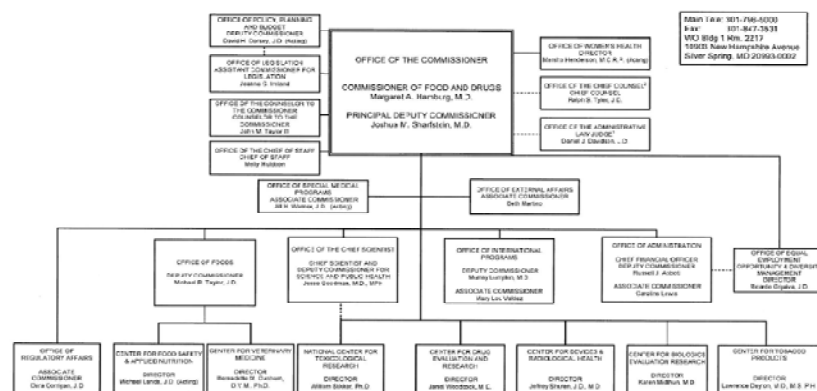
FDA OVERVIEW (cont.)

- Mission (cont.):
 2. “responsible for advancing the public health by helping to speed innovations that make medicines and foods more effective, safer, and more affordable; and helping the public get the accurate, science-based information they need to use medicines and foods to improve their health”

FDA OVERVIEW (cont. 2)

- 1950 – 2007 : various FD&C Act amendments and additional related acts are enforced
- Promulgated laws – described in Title 21 of Code of Federal Regulations (21 CFR), Parts 1 – 1299
[for electronic access, go to ecfr.gpoaccess.gov]
- Many subdivisions
- www.fda.gov

FDA ORGANIZATION



From: www.fda.gov/AboutFDA/CentersOffices/OrganizationCharts/default.htm

FDA ORGANIZATION (cont.)

FDA Subdivisions:

Subdivision	Responsibility
Office of the Commissioner	Program administration
Office of Regulatory Affairs	Enforces FDA regulations, monitors industry for compliance, recalls
Center for Biologics Evaluation & Research (CBER)	Assorted biological products/biologics (these replicate natural human substances): allergenic extracts for shots, blood & blood components, gene therapy products, transplant-related human tissue and cellular products, vaccines

FDA ORGANIZATION (cont. 2)

FDA Subdivisions (continued):

Subdivision	Responsibility
Center for Drug Evaluation & Research (CDER)	Drugs (purely chemical substances), therapeutic biological products (e.g. monoclonal Abs, cytokines, growth factors, enzymes, thrombolytics, proteins [natural or recombinant] extracted from animals for therapeutic use, non-vaccine therapeutic immunotherapies
Center for Devices & Radiological Health (CDRH)	Medical devices (e.g. catheters, breast pumps, contact lenses, lab instrumentation), diagnostic test kits, GMP, compliance, postmarket tracking, radiological health screening procedures (mammography, whole body CT scanning, medical imaging)

FDA ORGANIZATION (cont. 3)

FDA Subdivisions (continued):

Subdivision	Responsibility
Center for Food Safety & Applied Nutrition (CFSAN)	Various food products, GMOs, cosmetics, dietary supplements, infant formula, foodborne illness, food labeling & nutrition
Center for Veterinary Medicine (CVM)	Food additives and drugs given to animals; animals from which human foods are derived

BIOTECH PRODUCT JURISDICTION

Product Type	Center
Vaccine and blood product type therapeutic proteins	CBER
Some therapeutic biological products (mAbs for in vivo use, therapeutic proteins, cytokines and growth factors used as immunomodulators or alterers of cell production)	Transferred to CDER
Combination products (e.g. drug/device, biologic/device, drug/biologic, drug/device/biologic) – combined, packaged together, packaged separately but to be used together	CBER, CDER, or CDRH, dep on primary mode of action
Genetic tests for disease diagnosis or disease prevention, treatment, or cure	CDRH
Biosimilars (generic biologic, not identical to original)	CDER

REGULATED PRODUCT APPROVALS

Drugs

Application Type	Purpose
Investigational New Drug (IND)	To request exemption of approved marketing application for shipping new drug across state lines for clinical trials
New Drug Application (NDA)	To request approval to sell and market new drug in US; submitted with supporting documentation detailing drug ingredients; how drug is manufactured, processed, and packaged; results of animal studies and clinical studies; how the drug behaves in the body
Abbreviated New Drug Application (ANDA)	To request approval to sell and market generic drug in US; application need not include animal and clinical studies, but must show evidence that generic is bioequivalent to innovator drug

REGULATED PRODUCT APPROVALS (cont.)

Drugs ... 2

Application Type	Purpose
Over-the-Counter Drug (OTC)	Not an application; manufacturer can sell and market an OTC drug with FDA pre-approval if it conforms to the FDA-published OTC monograph; one monograph for each of 80 therapeutic classes of OTC drugs; monograph contains acceptable ingredients, doses, formulation, and labeling, and defines safety and effectiveness
Biologic License Application (BLA)	To request approval to sell and market biologic in US; like a NDA but for a biologic

REGULATED PRODUCT APPROVALS (cont. 2)

Medical Devices

Application Type	Purpose
Investigational Device Exemption (IDE)	To request exemption of approved marketing application for shipping investigational device across state lines for clinical trials; clinical trials typically required to support premarket approvals, but occasionally needed to support premarket notifications
Premarket Notification (PMN) / 510(k) Clearance	To request <u>clearance</u> to sell and market non-exempt Class I or Class II device in US that is substantially equivalent to a legally marketed (predicate) device
Premarket Approval (PMA)	To request <u>approval</u> to sell and market non-preamendment Class III device in US

REGULATED PRODUCT APPROVALS (cont. 3)

Medical Devices ... 2

Application Type	Purpose
Humanitarian Device Exemption (HDE)	To request exemption of certain requirements to sell and market humanitarian use device (HUD) in US that is intended to benefit patients through treatment or diagnosis of disease or condition affecting < 4,000 individuals per year; like a PMA but exempt from proof of effectiveness requirement

REGULATED PRODUCT APPROVALS (cont. 4)

Medical Device Notes

- Device classification:
 - o Dependent on **intended use** and **indications for use**
 - o Over 1,700 distinct devices, grouped into 16 medical specialty panels [per 21 CFR 862-892], have been classified
 - o 3 classes: Class I, Class II, and Class III, with regulatory control increasing from I to III – see:
<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Overview/GeneralandSpecialControls/default.htm>

REGULATED PRODUCT APPROVALS (cont. 5)

Medical Device Notes (cont.)

Device Class	Definition
Class I	• Low risk • Most (~74%) are exempt but non-exempt require PMN / 510(k) • Exempt manufacturers must still register establishment and list generic category or classification name • Exempt devices not exempt from GMP requirements; however, some are GMP exempt but not from records and complaint files • Some exempt devices have limitations to exemption status • Subject to general controls

REGULATED PRODUCT APPROVALS (cont. 6)

Medical Device Notes (cont.)

Device Class	Definition
Class II	- Moderate risk - Most are not exempt and usually require PMN / 510(k) - Some are exempt, but not from GMP requirements - Subject to general controls, and special controls to assure safety and effectiveness
Class III	- High risk - pose significant risk of illness or injury (devices usually support or sustain human life); OR not substantially equivalent to Class I or Class II predicate - Not exempt and require PMA unless a preamendment (pre May 28, 1976) device - Subject to general controls with PMA

REGULATED PRODUCT APPROVALS (cont. 7)

Medical Device Notes

- Substantial equivalence: if, in comparison to predicate
 - Has same intended use AND technological characteristics
 - Has same intended use BUT different technological characteristics that are supported by data that (1) shows device is at least as safe and effective as predicate AND (2) does not raise new safety and effectiveness questions

FDA WEB SITE RESOURCES

- Center–specific information for industry AND consumers
- About FDA
- Regulatory info & guidance documents
- Science & research
- News
- Recalls & alerts
- Approvals & clearances

DAY 2

FRIDAY, DECEMBER 17

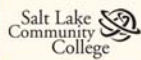


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REVIEW

1. What is a critical consideration during design / development? Why?
2. Provide 3 examples of “time costs \$\$\$”
3. Define: lean, just-in-time, & agile manufacturing
4. Name 3 types of manufacturing documents
5. Name one of the founding fathers of quality; what was his contribution?
6. The FD&C Act was prompted by what event?



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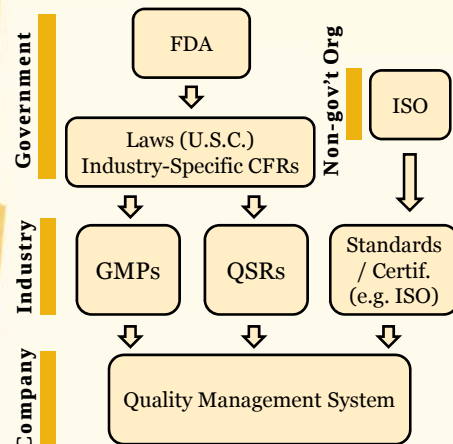
THE HIERARCHY

A tight relationship exists between

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- ☐ Good Manufacturing Practices (GMPs)
- ☐ Quality System Regulations (QSRs)
- ☐ Standards / Certifications (e.g. ISO)
- ☐ Quality Management System



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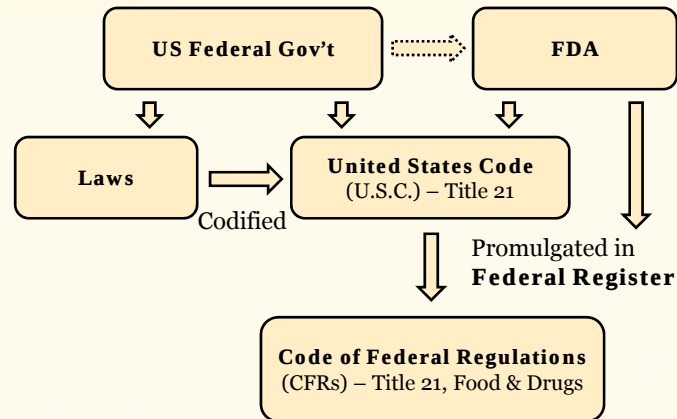
THE LAWS & CODE OF FEDERAL REGULATIONS



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LAWS → REGULATIONS



LAWS IMPACTING THE FDA

- **Food, Drug, and Cosmetic (FD&C) Act [1938]**
- **Kefauver-Harris Amendments [1962]** : inspired by thalidomide incident in Europe; strengthened rules for drug safety and required manufacturers to prove drugs' effectiveness
- **Medical Device Amendments [1976]** : resulted from US Senate finding that faulty devices caused 10,000 injuries, including 731 deaths; required safety and effectiveness safeguards

FD&C ACT OVERVIEW

- Chapter I: Short Title
- Chapter II: Definitions
- Chapter III: Prohibited Acts and Penalties
- Chapter IV: Food
- Chapter V: Drugs and Devices
- Chapter VI: Cosmetics
- Chapter VII: General Authority
- Chapter VIII: Imports and Exports
- Chapter IX: Miscellaneous

FD&C ACT OVERVIEW (cont.)

FD&C Act / U.S.C. section number cross-reference

[http://www.fda.gov/RegulatoryInformation/
Legislation/FederalFoodDrugandCosmetic
ActFDCAct/ucm086299.htm](http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/ucm086299.htm)

21 CFR OVERVIEW

Parts	Covers
100 series	Food – 110 cGMPs ; Dietary supplements – 111 cGMPs
200 & 300 series	Pharmaceuticals – 210 & 211 cGMPs
500 series	Animal feeds & medications
600 series	Biological products – 606 cGMPs
700 series	Cosmetics (limited regulations)
800 series	Medical devices – 820 cGMPs
900 series	Mammography quality requirements
1000 series	Radiation emitting device
1200 series	Non-FD&C Act rulings
Other	GLP – 58; GCP – 50, 54, 56; Electronic Records – 11

21 CFR 11

Electronic Records; Electronic Signatures

- 11.1 Scope
- 11.2 Implementation
- 11.3 Definitions
- 11.10 Controls for Closed Systems
- 11.30 Controls for Open Systems
- 11.50 Signature Manifestations
- 11.70 Signature/Record Linking
- 11.100 General Requirements
- 11.200 Electronic Signature Components and Controls
- 11.300 Controls for Identification Codes/Passwords

21 CFR 201

Labeling (select sub-parts)

- 201.1 Drugs; name and place of business of manufacturer, packer, or distributor
- 201.5 Drugs; adequate directions for use
- 201.15 Drugs; prominence of required label statements
- 201.17 Drugs; location of expiration date
- 201.117 Inactive ingredients
- 201.122 Drugs for processing, repacking, or manufacturing
- 201.128 Meaning of “intended uses”

21 CFR 314

Applications for FDA Approval to Market a New Drug (select sub-parts)

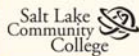
- 314.50 Content and format of an application
- 314.70 Supplements and other changes to an approved application
- 314.80 Postmarketing reporting of adverse drug experiences
- 314.102 Communications between FDA and applicants
- 314.126 Adequate and well-controlled studies
- 314.170 Adulteration and misbranding of an approved drug

21 CFR 610

General Biological Products Standards

(select sub-parts)

- 610.1 Tests prior to release required for each lot
- 610.9 Equivalent methods and processes
- 610.10 Potency
- 610.14 Identity
- 610.17 Permissible combinations
- 610.30 Test for Mycoplasma
- 610.44 Use of reference panels by manufacturers of test kits
- 610.60 Container label



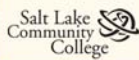
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21 CFR 803

Medical Device Reporting (select sub-parts)

- 803.9 What information from the reports do we disclose to the public?
- 803.12 Where and how do I submit reports and additional information?
- 803.16 When I submit a report, does the information in my report constitute an admission that the device caused or contributed to the reportable event?
- 803.17 What are the requirements for developing, maintaining, and implementing written MDR procedures that apply to me?



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21 CFR 1271

Human Cells, Tissues, and Cellular and Tissue-Based Products (select sub-parts)

- 1271.60 What quarantine and other requirements apply before the donor-eligibility determination is complete?
- 1271.85 What donor testing is required for different types of cells and tissues?
- 1271.150 Current good tissue practice requirements

21 CFR ?

21 CFR Parts can be viewed at

<http://ecfr.gpoaccess.gov/cgi/t/text/text-idx?c=ecfr&tpl=%2Findex.tpl>

GOOD <??> PRACTICES (GXP's)

DIFFERENT GXP's

- Good clinical practices (GCP) :
 - ✓ regulates clinical trials involving human subjects
 - ✓ protects human rights
 - ✓ provides assurance of safety and efficacy of developed product
- Good laboratory practices (GLP) :
 - ✓ regulates nonclinical laboratory studies that support FDA approval applications
- Good manufacturing practices (cGMP) :
 - ✓ regulates manufacture of products covered by FD&C

GOOD CLINICAL PRACTICES (GCP)

- Described in **21 CFR Parts 50, 54, and 56**
 - Protection of human subjects
 - Financial disclosure by clinical investigators
 - Institutional Review Boards (IRBs)
- Applies to clinical studies

GOOD LABORATORY PRACTICES (GLP)

- Described in **21 CFR Part 58**
- Applies mainly to preclinical studies, not to basic research
- However, can extrapolate to basic research

WHAT ARE GLPs?

- Examine GLP (21 CFR 58) up close . . .

See also :

1. Lab Compliance GLP tutorial

http://www.labcompliance.com/tutorial/glp/default.aspx?sm=d_a

2. WHO GLP Handbook (2009)

<http://apps.who.int/tdr/publications/training-guideline-publications/good-laboratory-practice-handbook/pdf/glp-handbook.pdf>

GOOD MANUFACTURING PRACTICES (GMP)

- Most stringently described in **21 CFR Parts**
 - **110** : for food
 - **111** : for dietary supplements
 - **210 & 211** : for drugs
 - **606** : for biologics
 - **820** : for medical devices (QSRs)
- Provides detailed requirements on how to operate manufacturing business
- Indirectly impacts R&D

WHAT ARE GMPs ?

- Example: [medical device cGMP](#) up close . . .

See also : FDA's CDRH Learn – *Quality System Regulation 21 CFR 820 Basic Introduction* presentation

<http://www.fda.gov/MedicalDevices/ResourcesforYou/Industry/ucm126252.htm>

GMP DESIGN CONTROLS

- Design Inputs & Outputs
- Design Verification : Outputs = Inputs
- Design Validation
- Compilation of records:
 - ☐ Design History File (DHF) : describes design history of finished product
 - ☐ Device Master Record (DMR) : contains procedures and specifications of finished device/product (“recipe”)
 - ☐ Device History Record (DHR) : contains production history of device/product

GMP REFERENCES

- FDA guidance documents:
 - o <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm064971.htm>
 - o <http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/General/ucm217665.htm>
 - o <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/PostmarketRequirements/QualitySystemsRegulations/MedicalDeviceQualitySystemsManual/default.htm>

GMP REFERENCES (cont.)

- asq.org
- <http://www.gmp-quality.com/index.html>

GXP COMPARISON ACTIVITY

Align 21 CFR Parts

- GLP
- drug GMP
- biologics cGMP
- medical device cGMP

BOTTOM LINE

GXPs = “best” practices

- ☐ defines what compliance requires
- ☐ does not describe exactly how to do it

ISO

ISO

- International Organization for Standardization :
non-governmental international standard-
setting body
- ISO promotes worldwide standards to :
 - ✓ Improve operating efficiency and productivity
 - ✓ Reduce costs
- See : <http://www.iso.org/iso/home.htm>

ISO 9000 STANDARDS

- A family of international standards that apply to quality system design and implementation
- Based on 8 quality management principles:
 1. Customer focus
 2. Leadership
 3. Workforce involvement
 4. Continuous improvement
 5. System approach to management
 6. Data-based approach to decision making
 7. Positive supplier communication / relationships
 8. Total process approach

ISO 9000 STANDARDS FAMILY

- ISO 9000:2005 *Quality management systems – Fundamentals and vocabulary*
- ISO 9001:2008 *Quality management systems – Requirements*
- ISO 9004:2009 *Managing for the sustained success of an organization – A quality management approach*

ISO 9000:2008 STANDARD – IN DETAIL

1. Scope
 - 1.1 General
 - 1.2 Application
2. Normative references
3. Terms and definitions
4. Quality management system
 - 4.1 General requirements
 - 4.2 Documentation requirements

ISO 9000:2008 STANDARD – IN DETAIL (cont.)

5. Management responsibility
 - 5.1 Management commitment
 - 5.2 Customer focus
 - 5.3 Quality policy
 - 5.4 Planning
 - 5.5 Responsibility, authority and communication
 - 5.6 Management review

ISO 9000:2008 STANDARD – IN DETAIL (cont. 2)

6. Resource management

6.1 Provision of resources

6.2 Human resources

6.3 Infrastructure

6.4 Work Environment

7. Product realization

7.1 Planning of product realization

7.2 Customer-related processes

7.3 Design and development



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ISO 9000:2008 STANDARD – IN DETAIL (cont. 3)

7.4 Purchasing

7.5 Production and service provision

7.6 Control of monitoring and measuring equipment

8. Measurement, analysis and improvement

8.1 General

8.2 Monitoring and measurement

8.3 Control of nonconforming product

8.4 Analysis of data

8.5 Improvement



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ISO 9000:2008 vs. GMPs

- Similarities ?
- Differences?

QUALITY MANAGEMENT SYSTEM

QUALITY MANAGEMENT SYSTEM (QMS)

- Enables a company to comply with FDA regulations / GXP
- *“Each manufacturer shall establish and maintain a quality system that is appropriate for the specific medical device(s) designed or manufactured, and that meets the requirements of this part.” – 21 CFR 820.5*

QUALITY MANAGEMENT SYSTEM (cont.)

- Quality management system is defined as *“the organizational structure, responsibilities, procedures, processes, and resources for implementing quality management” – 21 CFR 820.3*

KEY ELEMENTS OF QUALITY

- From Joseph Juran (late 1940s)
- **Quality planning** : designing a process capable of meeting quality standards
- **Quality control** : measuring a parameter, comparing to standard, taking action if not acceptable
- **Quality improvement** : finding a better way to meet specifications – dependent on good documentation / traceability

CONTROLLING & IMPROVING QUALITY

- Initiated by W. Edwards Deming (1940s - 50s)
- Keys:
 - ✓ Constantly improve production to **prevent** problems rather than correct them
 - ✓ **Distribute responsibility** throughout
 - ✓ Focus on **training and leadership**
 - ✓ Break down **communication** barriers: within company and with customers & suppliers
 - ✓ Use **statistical analysis** as basis for quality decisions

CONTROLLING & IMPROVING QUALITY (cont.)

- Depends on collecting and analyzing data via:
 - ✓ Inspection
 - ✓ Auditing (“independent” review)
 - ✓ Analysis (to determine action required)
 - ✓ Preventative action (PA) : for potential problems
 - ✓ Corrective action (CA) : for nonconformances
 - ✓ Verification and testing : follow-up after preventative or corrective action

QUALITY . . .

- **Assurance** : covers all activities relating to design, development, production, installation, servicing, and documentation (part of management)
 - ☐ Provides confidence that quality requirements will be met
 - ☐ **Plan – Do – Check – Act** (PDCA) approach
 - ☐ “Do it right the first time”
- **Systems Manual** : the company’s QUALITY

QUALITY . . . (cont.)

- **Engineering** : concerned with prevention planning and the correction of nonconformance with the production or service cycle
 - ❑ Analysis of manufacturing systems at all stages to improve production process quality and output
- **Control (Total quality control)** : inspection activities, tools, and skills
 - ❑ Ensures product meets customer's requirements, including reliability, maintainability, and safety

PRODUCT QUALITY

- **Begins with design** specifications & requirements
- Is the **responsibility of all employees**
- Quality Department has an important role
 - ❑ Quality assurance : “preventative” / “proactive”
 - ❑ Quality control : “corrective” / “reactive”
 - ❑ Quality engineering : “preventative” & “corrective”

PLAN-DO-CHECK-ACT CYCLE

- ISO standards' operating principle

PDCA Cycle :



- **Plan** : establish objectives & make plans to achieve them
- **Do** : implement plans (do what you planned)
- **Check** : measure results (i.e. measure/monitor how actual achievements meet planned objectives)
- **Act** : correct / improve plans and how they are implemented

CRITICAL QUALITY ACTIVITIES

- **Inspections**: of raw materials, subassemblies / intermediate products, final products, packaging
- **Materials management**: of inventory, purchases / requisitions, storage (quarantined vs. released vs. rejected)
- **Calibration**
- **Maintenance**
- **Documentation**: e.g. standard operating procedures, work instructions, batch records

QUALITY MANAGEMENT SYSTEM – REVISITED

- A plan focusing an organization's efforts on product quality and meeting customer needs
- Specifically:
“a set of policies, processes, and procedures required for planning and execution (of production / development / service) in the core business area of an organization”
[from: http://en.wikipedia.org/wiki/Quality_management_system]
- Provides a **process approach** for project execution

QUALITY MANAGEMENT SYSTEM – REVISITED (cont.)

- Enables an organization to **identify, measure, control, and improve** various core processes that will lead to improved business performance
- Essentially, what an organization implements to manage processes/activities so that the products meet the organization's objectives:
 - **Satisfying customer requirements**
 - **Complying with regulations**
- Usually designed to **meet ISO standards**

QUALITY MANAGEMENT SYSTEM – REVISITED (cont. 2)

- Also based on FDA regulations (cGMPs / QSRs)
- QMS should include methods of :
 - ✓ Training & qualifying personnel
 - ✓ Controlling product design
 - ✓ Controlling documentation & records
 - ✓ Controlling purchasing
 - ✓ Identifying & tracing product at all production stages
 - ✓ Defining & controlling production & processes
 - ✓ Defining & controlling inspection / measuring / test equipment

QUALITY MANAGEMENT SYSTEM – REVISITED (cont. 3)

- ✓ Validating processes
- ✓ Accepting product
- ✓ Controlling nonconforming product
- ✓ Instituting corrective & preventative actions
- ✓ Controlling labeling & packaging
- ✓ Servicing production equipment
- ✓ Using statistical techniques
- These aspects are evaluated for ISO certification (by independent, accredited body)

QUALITY MANAGEMENT SYSTEM – RECAP

- Identifies needed processes
- Determines sequence & interaction
- Develops methods to determine process effectivity
- Ensures resources & info are available to support processes
- Monitors, measures, & analyzes processes
- Implements actions to achieve planned results
- Continually improves processes

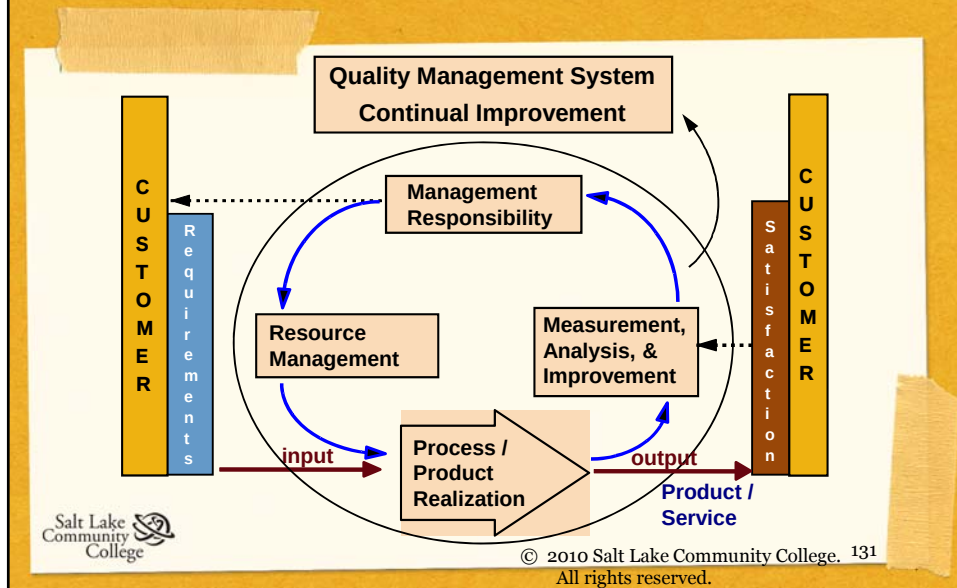


ISO 9001 REQUIREMENTS FOR A QMS STRUCTURE

1. Scope
2. Normative References
3. Terms & Definitions
- 4. Management System**
- 5. Management Requirements**
- 6. Resource Requirements**
- 7. Product & Service Realization**
- 8. Measurement, Analysis, & Improvement**



QMS PROCESS MODEL



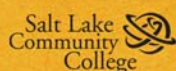
ISO 9001 REQUIREMENTS FOR A QMS STRUCTURE

1. Scope
2. Normative References
3. Terms & Definitions
4. **Management System**
5. **Management Requirements**
6. **Resource Requirements**
7. **Product & Service Realization**
8. **Measurement, Analysis, & Improvement**



DAY 3

SATURDAY, DECEMBER 18

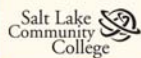


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REVIEW

1. What is the relationship between USC and CFR?
2. Where can you find the CFR?
3. What is the purpose of GLP ? GCP ? cGMP ?
4. What part(s) of 21 CFR describe GLP ? cGMP for drugs? cGMP for biologics? cGMP for medical devices? cGMP for dietary supplements?
5. On what 8 quality management principles are the ISO 9000 standards based?



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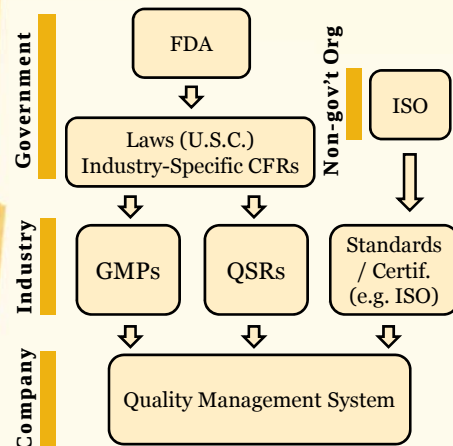
THE HIERARCHY

A tight relationship exists between

- ☐ the FDA [regulating body]
- ☐ the Laws [US Code]
- ☐ the Code of Federal Regulations (CFRs) - gov't agency promulgated
- ☐ Good Manufacturing Practices (GMPs)
- ☐ Quality System Regulations (QSRs)
- ☐ Standards / Certifications (e.g. ISO)
- ☐ Quality Management System



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UNDERSTANDING TEAMS

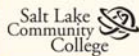


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A TEAM IS . . .

- Group of organized individuals **working toward a common objective**
- Small number of people **equally accountable for accomplishing a task or goal**
- Small number of people w/ **complementary skills committed a common purpose**
- Combines individuals' knowledge, experience, skills, & attitude for a **synergistic effect**



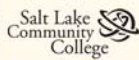
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A TEAM IS NOT . . .

- An **rganizational** work unit
- A crowd of people or informal gathering
- A club, association, or society
- An organization's management
- Staff meetings, conferences, seminars, or courses

**Unless the above are
functioning as a TEAM**



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WHEN IS A TEAM NEEDED ?

The objective involves more than one organization or function (Purchasing, Inspection, Stores)

A degree of isolation from the rest of the organization will help maintain focus on the objective or problem (long term project)

People w/ specific training & experience must be on-call when a need or problem arises that requires their skills (proposals, design reviews)

TEAM VALUE

No team should be formed unless its purpose supports the organization's strategies, plans, & objectives



HOW LONG SHOULD A TEAM BE IN EFFECT ?

- Predetermined period
- Resource availability
- Team's purpose
- Progress being made
- Value of the planned outcome
- Team's effectiveness



TEAM MEMBER ROLES

- **Champion** - Advocate who initiates a concept or idea for change
- **Sponsor** – Backer who supports the team
- **Team Leader** – Change agent who:
 - Staffs the team
 - Participates
 - Takes responsibility
 - Handles logistics
 - Entrusted to lead
 - Communicates w/ mgt
 - Has authority
 - Responsible for records



TEAM MEMBER ROLES (cont.)

- **Facilitator** – Helper/advisor who:

Observes team processes & suggests changes to Leader

Intervenes when multiple conversations develop

Prevents individual from dominating the team

Assists Leader in closing discussions

May provide team with training



TEAM MEMBER ROLES (cont. 2)

- **Time Keeper** – Monitor who helps team keep track of time

- **Scribe** – Note taker who records critical data/ formal minutes (if required) & distributes it

- **Team Members** – Participants/subject matter experts who work together to bring about change or improvement



TEAM PERILS & PITFALLS

- Team mission not linked to organization's strategic direction or goals
- Lack of management commitment
- Members lack the needed competence
- Inadequate leadership
- No team building
- Rules nonexistent or inadequate
- And many, many more



WHAT MAKES A TEAM WORK?

All members:

- Agree on the expected outcomes
- Accept their assigned responsibilities
- Have access to what is needed to get the job done; information isn't hoarded
- Are clearly committed & understand their roles
- Feel they are making a difference
- Manage conflicts



TEAM STAGES – 1. FORMING

Members are trying to establish their position on the team

- ✓ Be clear about the purpose of the team
- ✓ Identify members' roles
- ✓ Establish criteria for acceptable behavior

TEAM STAGES – 2. STORMING

Members are still acting as individuals

Defenses are still up

Uncertainty may still exist

- ✓ A good team leader can be vital to keeping the team focused on their goal rather than redefining it

TEAM STAGES – 3. NORMING

Members shift from dwelling on personal agendas
& address the objectives of the team

The team gets rolling

- ✓ Potential danger : members may withhold ideas for fear of reintroducing conflict
- ✓ A good facilitator can use various tools & techniques for drawing members out

TEAM STAGES – 4. PERFORMING

Members understand the strengths & weaknesses
of each member

Progress is clear & achievement of the goals /
objectives is in sight

Note: a team may drop back to an earlier stage if
something disturbs its growth

TEAM BARRIERS



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- Conflict can occur at any point, but is more common during the “forming” & “storming” stages
- Conflict can be positive – a sign of change or movement
- Approach conflict as an opportunity to learn & move forward

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UNDERSTANDING TEAMS ACTIVITY

- Self-assessment – from :
<http://www.petermerrill.com/self-assessment>
- Complete self-assessment
- Tally scores
- Determine your best role(s)
- Discuss results with group

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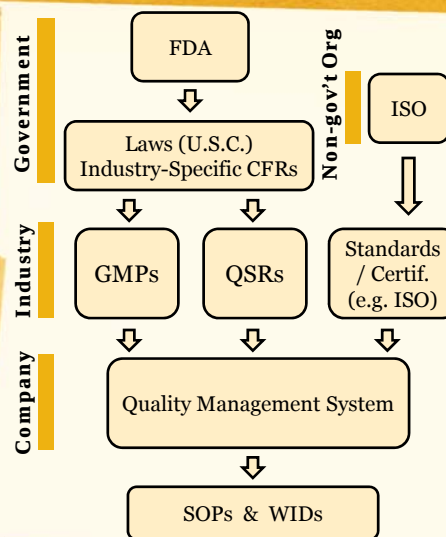
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WHAT DOES THIS HAVE TO DO WITH QMS?

- Keys to quality, from Deming:
 - ✓ Constantly improve production to **prevent** problems rather than correct them
 - ✓ **Distribute responsibility** throughout
 - ✓ Focus on **training and leadership**
 - ✓ Break down **communication** barriers: within company and with customers & suppliers
 - ✓ Use **statistical analysis** as basis for quality decisions

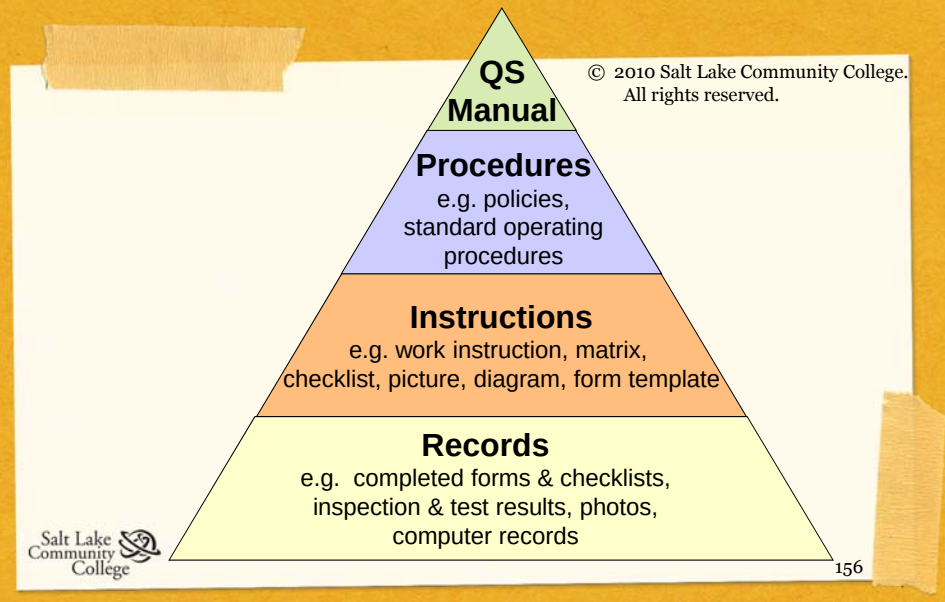
THE “TRICKLE DOWN” EFFECT

A company's set of Standard Operating Procedures and Work Instruction Documents is derived from its quality management system, and all laws & regulations, industry guidances, standards governing QMS's



QMS DOCUMENTS

QMS DOCUMENTS



QMS DOCUMENTS (cont.)

- Examine samples of
 - ✓ **Quality systems manual**
 - ✓ **Procedures – SOP**
 - ✓ **Instructions – WID**
 - ✓ **Records – Batch record**

QMS vs. SOPs & WIDs

- Can think of:
 - ☐ Quality management system as the “rule book”
 - ☐ SOPs & WIDs as the “play book”

WRITING QMS DOCUMENTS

SOP & WID ELEMENTS

- Organization identification : logo, name, address
- Document ID number (could be optional)
- Revision number
- Effective date
- “Page X of Y”
- Title of document : should describe activity
- Document approval table
- Document history table

SOP & WID ELEMENTS (cont.)

- Sections as appropriate:
 - ✓ Purpose
 - ✓ Scope
 - ✓ Responsibilities
 - ✓ References
 - ✓ Definitions
 - ✓ Points / policies
 - ✓ Attachments
 - ✓ Precautions
 - ✓ Equipment & Materials
 - ✓ Procedure / instructions
 - ✓ Acceptance criteria

CONSIDERATIONS

- Writing SOPs / WIDs is an art
- Understand the documents' users / readers
- *Specifically vague* vs. *Vaguely specific*
- Vague-idize to provide controlled flexibility but maintain consistency
- Mentally picture the instructions being used
- Provide enough detail to yield the desired outcome when the instructions are followed
- What is written is exactly how it will be done

DOCUMENT WRITING ACTIVITY

- Form groups
- Each group will be assigned to write one biotech WID and the complementary batch record
 - o First, each person in group write a first draft
 - o Then, compare with the rest of your group to create / finalize the “best” WID and batch record

DAY 4

SUNDAY, DECEMBER 19



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REVIEW

1. What is the difference between ISO 9000, 9001, and 9004?
2. Per ISO 9001:2008, how must a QMS be structured?
3. What are the typical stages of a team?
4. How might having an understanding of teams and of how you might function on one benefit an organization?
5. What are the typical QMS document categories?

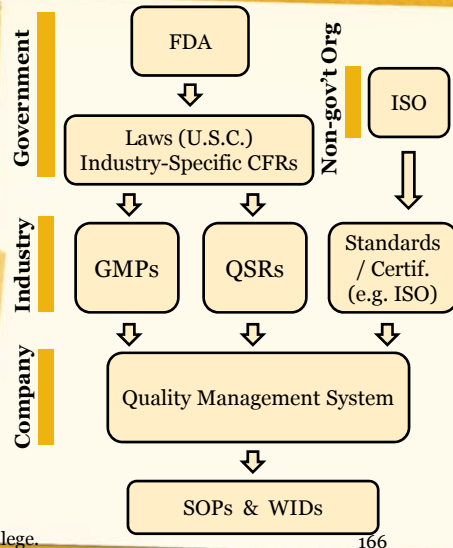


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THE “TRICKLE DOWN” EFFECT

A company's set of Standard Operating Procedures and Work Instruction Documents is derived from its quality management system, and all laws & regulations, industry guidances, standards governing QMS's



VALIDATING QMS DOCUMENTS

DOCUMENT VALIDATION ACTIVITY

- Groups will trade the best WID / batch record set with one of the other groups as directed
- Each group of 4 will split into 2 pairs
- Each pair will independently validate their assigned WID / batch record set by using them

QMS DOCUMENTS – DISCUSSION & DEBRIEF

- Discuss results of document validation
- Lessons learned ?
- Best practices ?

SETTING UP A QUALITY MANAGEMENT SYSTEM

- Considerations
 - ✓ Critical needs vs. “wish list”
 - ✓ Which “piece(s)” / “level(s)” first ?
 - ✓ Practicality
 - ✓ “Extra effort” vs. “Realized gains”
 - ✓ It’s hardest to start & gets easier with progress
 - ✓ For education / training : what level of compliance to strive for ?
- Discussion

SETTING UP A QUALITY MANAGEMENT SYSTEM (cont.)

- Example:

BMAN 2110 – Good Manufacturing Practices
Project (Spring 2010):

QMS Component + Documentation for HeLa
Production (Idaho Technology Inc.-
contracted InnovaBio project)

ADDITIONAL VOCABULARY

- Lean manufacturing terms
- Six Sigma: LCL & UCL > 4.5 σ away from μ
(long term tracking, -1.5 σ accounts for variation)
http://en.wikipedia.org/wiki/Six_sigma
- FDA inspection : Form 483 documents
inspectional observations (great as case studies!)
Public access to these reports from FDA's ORA FOIA
Electronic Reading Room :
<http://www.fda.gov/AboutFDA/CentersOffices/ORA/ORAElectronicReadingRoom/default.htm>

GENERAL Q & A SESSION

- Unanswered questions ?
- Confused still ?
- How to apply what you've learned ?
- Other ?

WRAP-UP & EVALUATION

- Recap of training
- Evaluation of training by participants

APPENDICES

LIST OF APPENDICES

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Peter's Pills Production Plant

Peter is the owner of Peter's Pills. The company manufactures pills for treatment of assorted conditions such as having bad hair days and wearing mismatched shoes.

Peter is interested in improving his manufacturing process & his profitability.

As his design manufacturing team, your job is to develop a new production line for him. Do this by constructing a new production line using the marble maze kit, and then testing the line by producing batches, each one consisting of 6 pills (marble runs). Analyze the results of these batches to determine the profitability of your production line.

See the instructions on the "Controlling Variation" page for details on how to do this.

Your goal is make 8 batches of 6 pills each, and see if you can consistently turn a high profit.

Here is the cost schedule related to testing the new production line.

Income

Action	Income
Income per pill successfully made (marble completes the maze)	\$100 / pill

Expenses

Action	Expense
Cost to develop & build maze	\$1500
Minor design change (tighten or adjust a piece)	\$50 / piece
Redesign (move a piece to a different location)	\$100 / piece

Controlling Variation

The purpose of this exercise is to illustrate the difference between **tampering** and **controlling variation**.

1. Identify Your Role : Builder(s), Analyst(s), Observer(s), and Recorder

2. Builders – Build Production Line

- Production line = marble maze
- Must use all enclosed parts in the production line
- Cannot use any parts not included in the set

3. Analysts & Observers – Make Pills

- Make 1 batch of 6 pills (let 6 marbles run through maze) & record your results on the **Check Sheet**, capturing number of pills made successfully, income generated by this, expenses, and net profit so far
- Carefully observe this first batch, identifying any problems areas in the production line (e.g., marbles jumping out of the maze, getting stuck, not following the correct path, etc.)
- **Do not make any changes!**

4. Recorder – Record Observations

- Record the number of pills in the first batch that were properly made (finished maze in the appropriate place) on the **Check Sheet**
- Record any areas of difficulty with the production line (maze/marbles) under **Observations / Analysis**

5. Entire Team – Analyze the Observations

- Identify the problem spots
- Determine what production line changes to make & make these changes to the maze
- Record your changes on the **Check Sheet** under the **Observations / Analysis** column

6. Make Another Batch of Pills

- Repeat steps 3-5

7. Make More Batches of Pills

- Decide strategy listed below your team will use (combinations OK) and note on **Check Sheet** under the **Strategy** column:
 - Managing Variation – Repeat steps 3-5 without changes or adjustments
 - Minor design changes (tightening & tweaking) – Make 1 batch at a time, but tweak your line as needed after each run.
 - Redesign (moving pieces around) – Make 1 batch at a time, but redesign as needed after each run
- Make a total of 8 batches – if the first batches were “catastrophic”, you may make up to 10 batches

8. Analyze Your Batches

- Were your later batches better than your earlier ones?
- Did you manage your variation or tweak as you went?
- Write your conclusions on the **Check Sheet**.

Check Sheet

Number of pills produced successfully in each batch :

Batch #:	1	2	3	4	5	6	7	8	9	10
# Pills Produced:										

Observations & Costs associated with each Batch :

Batch #	Observations / Analysis	Strategy	Income	Expenses	Net Profit
1					
2					
3					
4					
5					
6					
7					
8					
9					
10					

Conclusions :

Total # of Batches Made: _____

Overall Profit : \$ _____

NOTES :

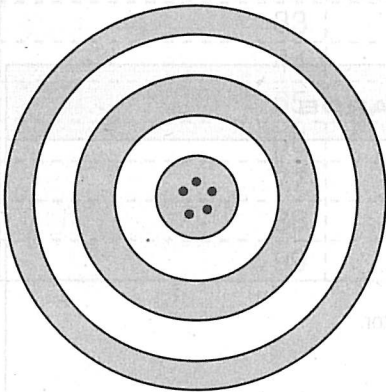
Using Statistical Process Control Charts

Every process includes a certain amount of variation. Depending on the amount and type of variation, the process may be either in control or out of control. When it is in control, the variation is attributed to random causes and when it is out of control, the variation is attributed to specific, or assignable, causes. Statistical process control (SPC) charts are used to analyze the variation within a process. SPC gives frontline workers a tool to determine when a statistically significant change has taken place in the process or when a seemingly significant change is just due to chance causes.

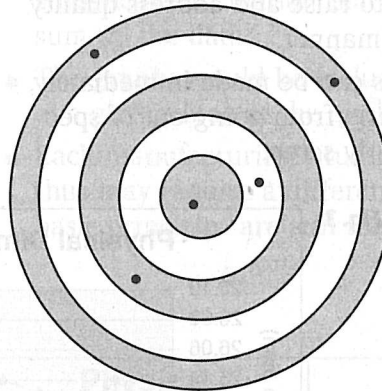
Random Variation

The terms “in control” and “out of control” refer only to whether the process is operating within the range of random variation. They do not correspond to products meeting or failing to meet specifications. As an illustration of this concept, consider two archers, one an expert and the other a novice, at a target range. You would expect the expert’s target to look like the target in **Fig. 1**, with all the holes in or near the bull’s-eye. The novice tends to have wide variation, as in the target in **Fig. 2**. Even though the scores are very different, both processes are in control, because the variations due to random differences in how the arrow is fired are consistent with past results for the two archers.

■ **Fig. 1** Expert in control



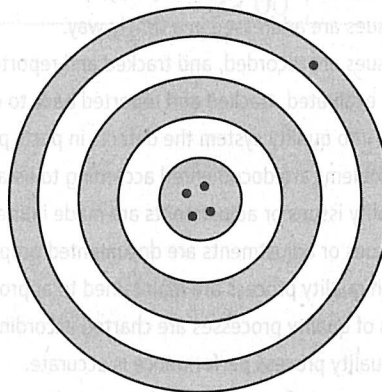
■ **Fig. 2** Novice in control



Assignable Variation

Now consider the target in **Fig. 3**, which is the expert’s second target of the day. Four holes are in the bull’s-eye, but the final shot is well off the mark. Although the target scores much better than that of the novice, it indicates that something was out of control. Perhaps the archer was distracted or had a muscle cramp. In either case, the unusual result can be attributed to an assignable cause and is statistically out of control.

■ **Fig. 3** Expert out of control



(continued on next page)

Analyzing SPC Charts

SPC charts plot the value for one process parameter and analyze the variation. Key values used to determine whether the process is in control are:

- The center line (CL).
- The upper control limit (UCL).
- The lower control limit (LCL).

Statistical equations, using historical data for the process, are used to determine these values. You will probably not be responsible for determining these values. In most cases, a statistician, engineer, or even a computer program provides them. Frontline workers then use the data to chart the process. If you are required to know how to perform statistical analysis in more depth than discussed in this worksheet, your employer will schedule training, either on site or through classroom instruction.

The parameters that you plot on an SPC chart depend on the process. They can include the amount of time spent on a step, the number of defects in a lot of products, dimension measurements of a part, or anything else about a process that can be measured. Decisions about what to measure, sample size, and sample frequency are based on the process itself.

In Control or Out of Control

Frequent adjustments and changes to equipment do not necessarily improve a process. In fact, adjustments to a process that is in control can be a source of assignable variation, causing the process to be out of control. To determine whether a process is out of control, you analyze the plotted results on the SPC chart. If the process is in control, you continue to monitor it. If it is out of control, you must identify the assignable causes, correct them, and continue to monitor the process to determine whether the change has brought it back into control.

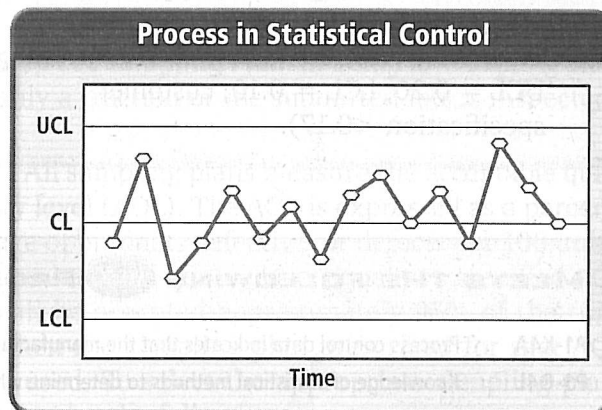
There are several different indications that the process is out of control, based on data falling outside the control limits or process trends that indicate

a steady or cyclical change in conditions. The most common tests for assignable variation are:

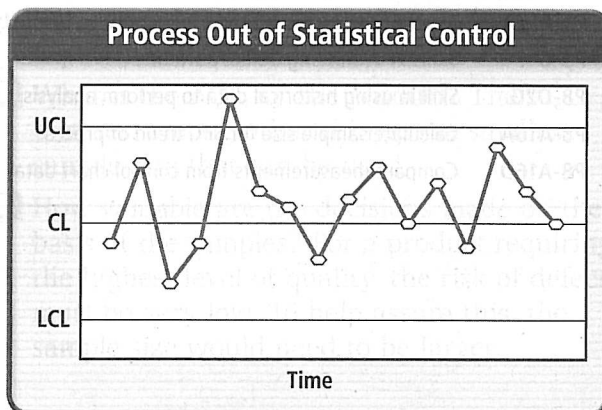
- 1 data point falling outside the control limits.
- 6 or more points in a row steadily increasing or decreasing.
- 8 or more points in a row on one side of the center line.
- 14 or more points alternating up and down.

For example, examine the charts in Fig. 4 and Fig. 5, which plot process time. The process in Fig. 4 is in control, because data points are within the control limits, and data points are randomly distributed, showing no trends. The process in Fig. 5 is out of control, because one of the data points falls above the UCL.

■ Fig. 4



■ Fig. 5



(continued on next page)

APPLYING YOUR KNOWLEDGE

For each of the following processes, create a control chart for the data provided. Determine whether the process is in control and explain why.

- Run time measurements, in hours:
2, 2.5, 1.75, 2.25, 2, 1.75, 1.75, 2.25
(CL = 2 h, UCL = 2.75 h, LCL = 1.25 h).
- Part length in mm: 33.9, 33.0, 33.2, 33.5, 33.7, 33.6, 33.5, 33.8, 33.4
(CL = 33.4 mm, UCL = 33.8 mm, LCL = 33.0 mm, customer specification = 35 ± 0.5 mm).
- Contaminants in product, in percent:
0.15, 0.19, 0.11, 0.13, 0.14, 0.16, 0.17, 0.18, 0.19, 0.13, 0.19 (CL = 0.15, UCL = 0.20, LCL = 0.10, customer specification < 0.17).

PRODUCTION CHALLENGE

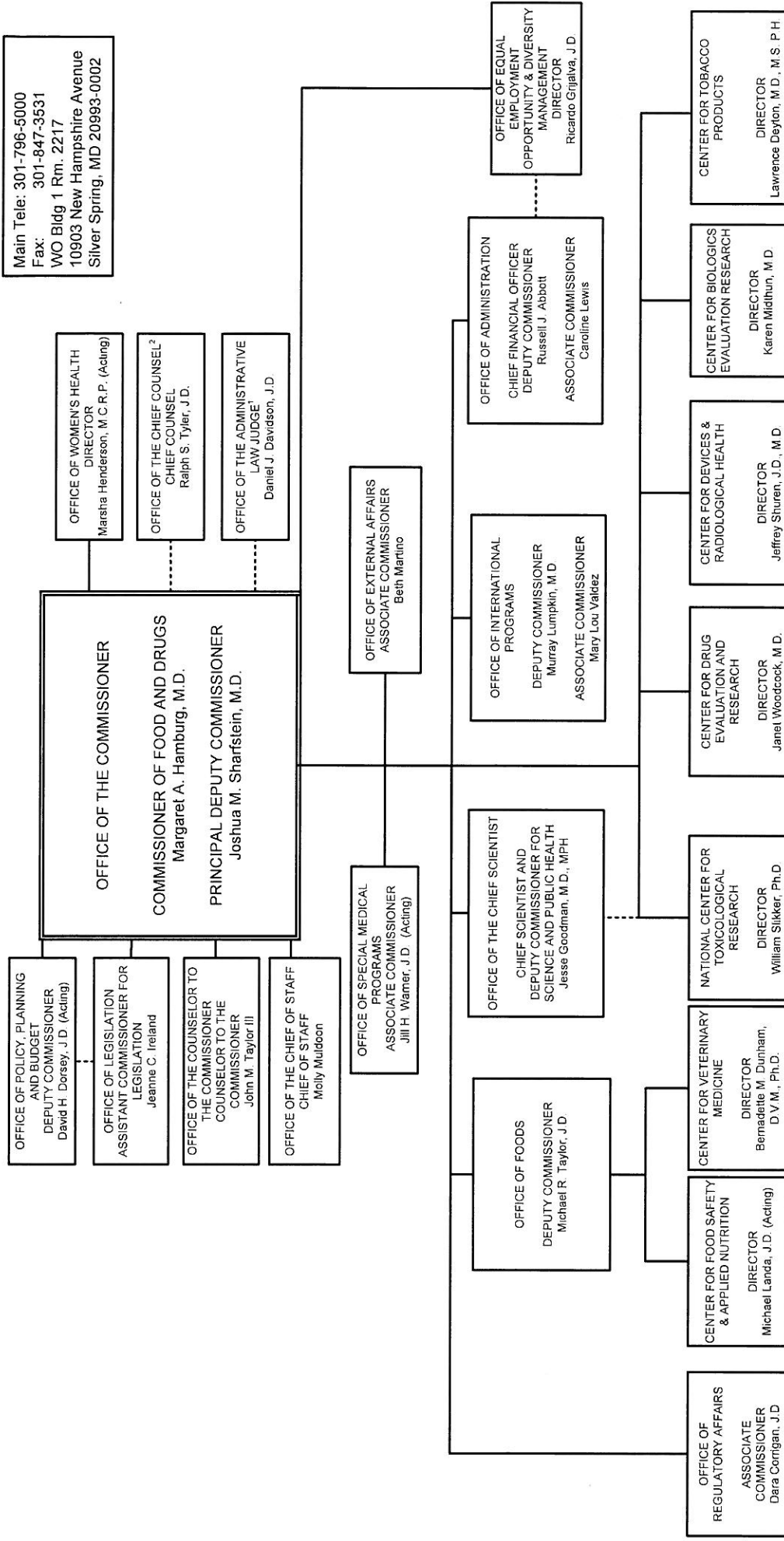
Your company produces contact cement. During the production process, the solvent toluene is mixed with an adhesive base to make the contact cement spreadable. How would SPC be used to ensure that this mixing process is in control?

MEETS THE FOLLOWING PRODUCTION STANDARDS

P1-K4A	Process control data indicates that the manufacturing process is in compliance with standards.
P1-04L	Knowledge of statistical methods to determine when process is out of control.
P1-A14D	Complete SPC chart.
P4-A11A	Take a course on quality tools used by the company (e.g., SPC or statistics).
P4-A11B	Attend classes on SPC.
P4-A16A	Use math to produce charts on department quality levels.
P8-01F	Skills in evaluating defect patterns.
P8-02G	Skill in using historical data to perform analysis.
P8-A16A	Calculate sample size for SPC trend of process.
P8-A16D	Compare measurements from control chart data.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION



Carroll *Stark* 9/21/10

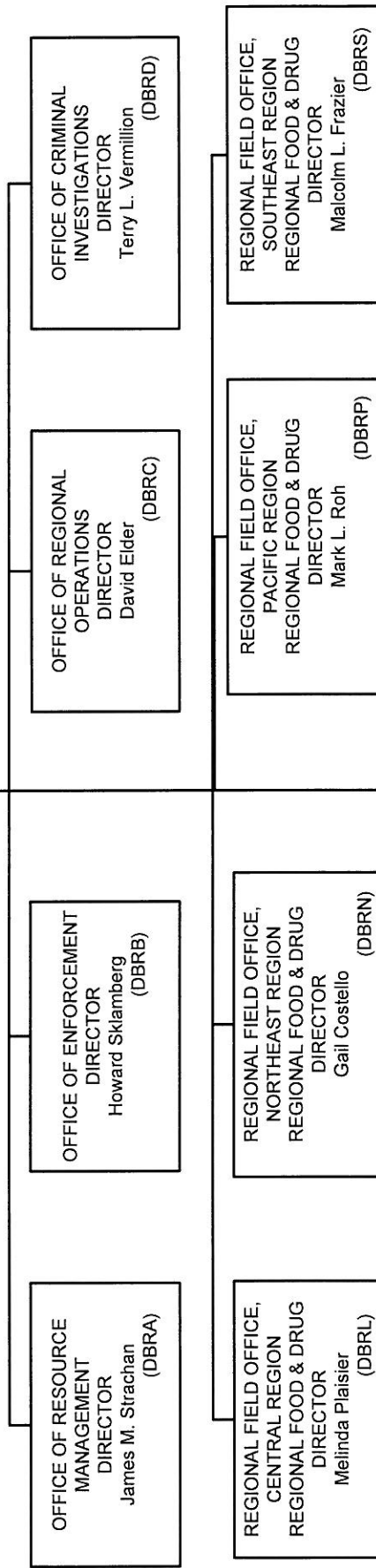
¹ Reports Directly to the Secretary, HHS
² Reports to the General Counsel of the HHS, advises the Commissioner of Food and Drugs

Approved by the FDA Reorganization Coordinator and Principal Delegation Control Officer

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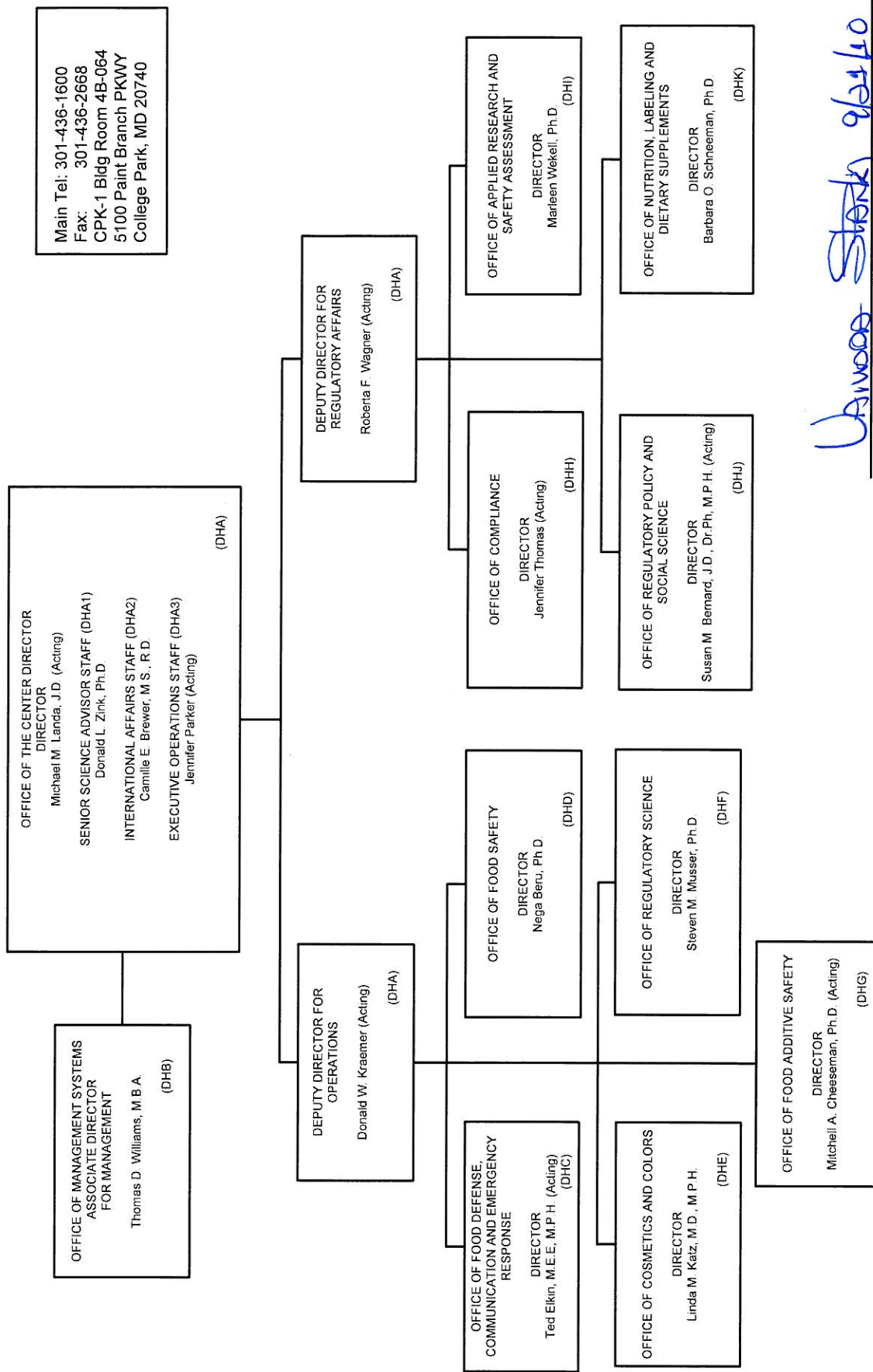
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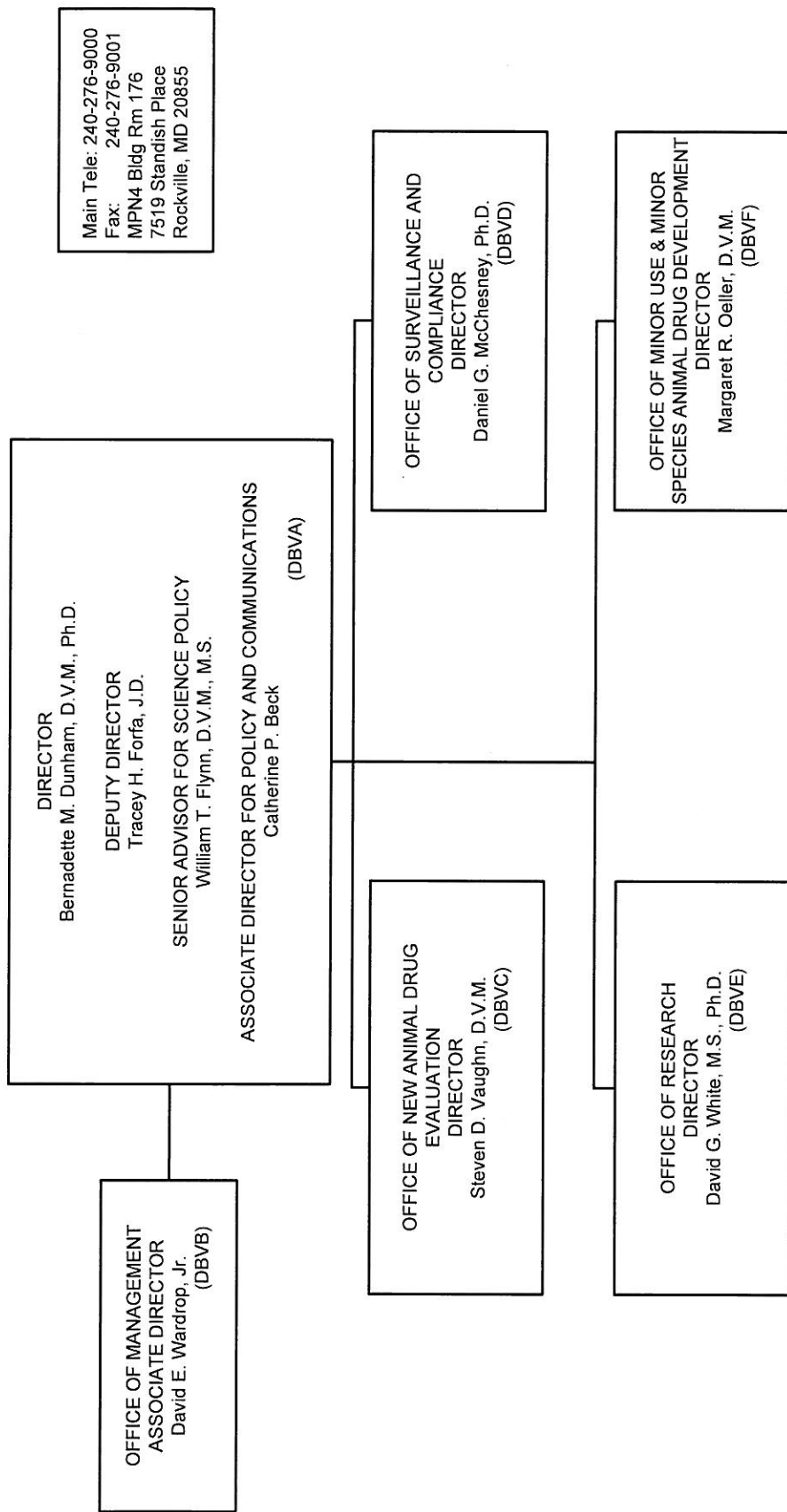


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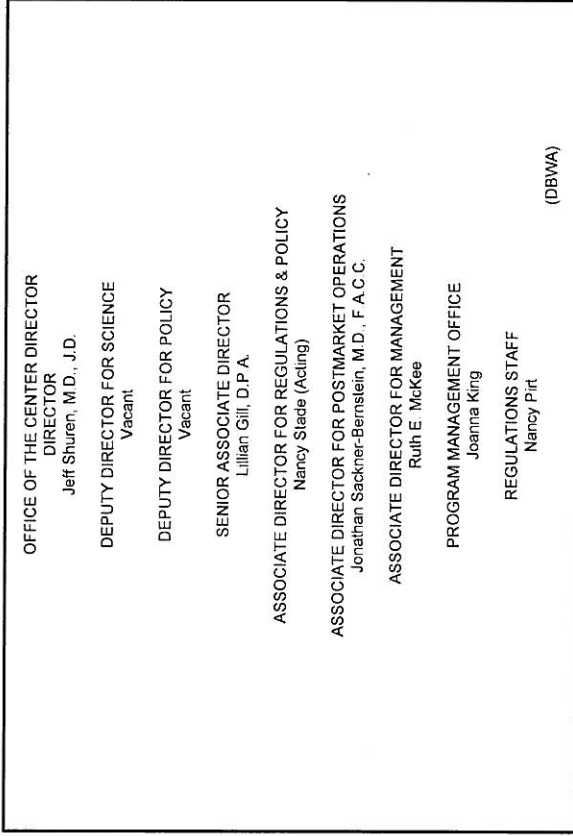
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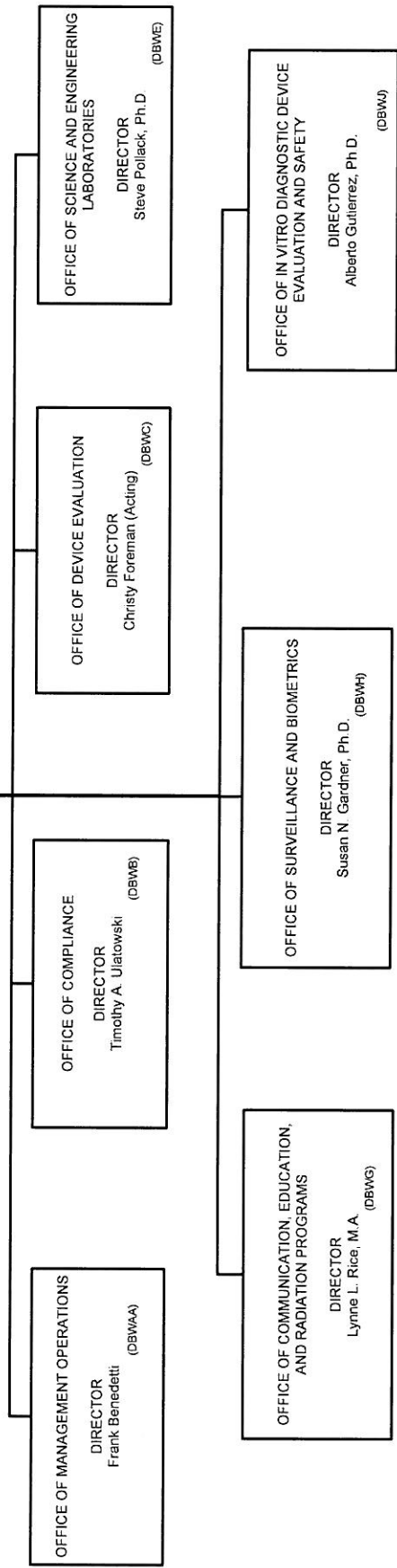


Principal Deposition Control Officer

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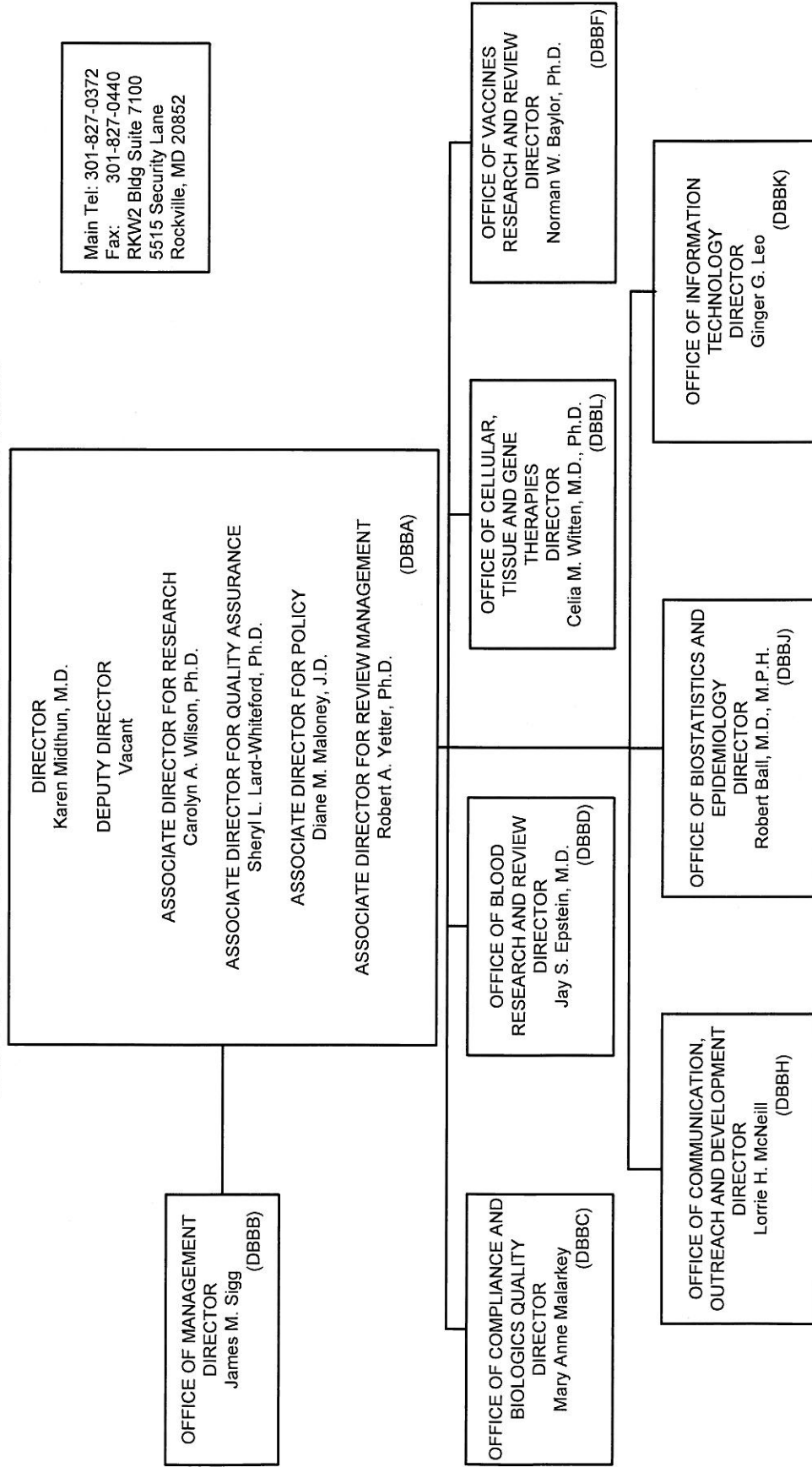
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DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR BIOLOGICS EVALUATION AND RESEARCH



Vanessa S. [Signature] 9/21/10

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Good Laboratory Practice Regulations

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Introduction and Objectives and Key Requirements

Good Laboratory Practice (GLP) deals with the organization, process and conditions under which laboratory studies are planned, performed, monitored, recorded and reported. GLP practices are intended to promote the quality and validity of test data.

Published GLP regulations and guidelines have a significant impact on the daily operation of an analytical laboratory.

GLP is a regulation. It is not only good analytical practice. Good analytical practice is important, but it is not enough. For example, the laboratory must have a specific organizational structure and procedures to perform and document laboratory work. The objective is not only quality of data but also traceability and integrity of data. But the biggest difference between GLP and Non-GLP work is the type and amount of documentation.

For a GLP inspector it should be possible to look at the documentation and to easily find out

- who has done a study,
- how the experiment was carried out,-
- which procedures have been used, and
- whether there has been any problem and if so
- how it has been solved.

And this should not only be possible during and right after the study has been finished but also 5 to 10 or more years later.

Frequently the question comes: how much does this cost? It has been estimated that these additional organizational and documentation requirements increase operational costs of up to 30% compared to non-GLP operation.

The key requirements of a GLP type works are

- Responsibilities should be defined for the sponsor management, for study management and for the quality assurance unit.
- All routine work should follow written standard operating procedures.
- Facilities such as laboratories should be large enough and have the right construction to ensure the integrity of a study, for example, to avoid cross contamination.
- Test and control articles should have the right quality and instruments should be calibrated and well maintained
- People should be trained or otherwise qualified for the job
- Raw data and other data should be acquired, processed and archived to ensure integrity of data.

Unfortunately most laboratories are in situations where they have had to interpret the regulations. Procedures have been developed on an ad hoc basis, in isolation, in response to inspections by both their company's Quality Assurance Unit and regulatory bodies.

Under such duress, many scientists in industry have developed procedures to validate their instrumentation even though the same approach will already have been applied at the instrument manufacturer's site. Standard operating procedures written to accompany such validation efforts often duplicate extracts from operation manuals —why don't the manufacturers provide the SOPs directly? When it comes to validating the instrument's application software, the person responsible has to take the manufacturer's word for it that the software has been validated and hope that supporting documents, such as test results and source code are available to regulatory agencies upon request.

This tutorial should help to understand requirements and with the help of SOPs and examples offered by Labcompliance, to implement requirement in a most cost effective way.

History of GLP and Relation to other Regulations

National Legislation

Various national legislation, e.g., the Federal Food, Drug, and Cosmetic Act in the United States places the responsibility for establishing the safety and efficacy of human and veterinary drugs (and devices) and the safety of food and color additives on the sponsor (manufacturer) of the regulated product. Public agencies (the United States government's Food and Drug Administration, FDA, for example) are responsible for reviewing the sponsor's test results and whether or not they can demonstrate the product's safety and efficacy. Only when the agencies are satisfied that safety and efficacy have been established adequately is the marketing of the product permitted.

Fraud and misinterpreted data

Until the mid-1970s, the underlying assumption at the FDA was that the reports submitted by the sponsors to the agency accurately described study conduct and precisely reported the study data. A suspicion that this assumption was mistaken was raised during review of studies submitted by a major pharmaceutical manufacturer in support of new drug applications for two important therapeutic products. Data inconsistencies and evidence of unacceptable laboratory practices came to light. The FDA requested a "for cause" inspection of the manufacturer's laboratories to determine the cause and the extent of the discrepancies (a "for cause" inspection is one initiated at the request of an agency when there are grounds for doubt surrounding an FDA regulated product), and revealed defects in design, conduct, and reporting of the studies. Further inspections at several other sites found similar problems.

FDA's Reaction

The conclusion that many of the studies on which proof of safety of regulated products had been based could indeed be invalid alarmed the FDA, the United States Congress, the public, and industry. Task forces were soon formed to develop ways and means of ensuring the validity and reliability of all non-clinical safety studies submitted for FDA decision making. They would eventually publish standards for measuring the performance of research laboratories and define an enforcement policy.

Good Laboratory Practice (GLP) regulations were finally proposed on November 19, 1976 for assuring a

study's validity. The proposed regulations were designated as a new part, 3.e., of Chapter 21 of the Code of Federal Regulations. The final regulations were codified as Part 58 (21CFR).

EPA's Reaction

The United States Environmental Protection Agency (EPA) issued almost identical regulations in 1983 to cover the required health and safety testing of agricultural and industrial chemicals under the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA)⁴ and the Toxic Substances Control Act (TSCA),⁵ respectively. The GLPs were promulgated in response to problems encountered with the reliability of submitted studies. Some of the studies were so poorly conducted that "the resulting data could not be relied upon for the EPA's regulatory decision making process."⁶ The EPA regulations were extensively amended in 1989 and now cover essentially all testing required to be submitted to EPA under either Act.^{7, 8} Both GLP regulations are of a similar format and have, with few exceptions, the same wording.

Even though GLPs were only issued for these two specific official programs, the possession of sound data is an equally important consideration for Agency decision makers in all EPA programs to protect public health and the environment. We can thus expect the GLP regulations to be more widely adopted — the Office of Solid Waste has included GLP terms in its contracts for reproductive toxicology studies. For example, GLP regulations have been transferred under the umbrella of the OECD as principles of Good Laboratory practices to other countries like Europe and Asia .

Applicability and Relation to other Regulations

GLP vs. GCP, GMP and Part 11

Figure 1 illustrates how so called Good Practices regulations correlate to the life of a drug, starting from basic research and drug discovery on the left side through preclinical development in the middle and clinical trials and manufacturing at the right

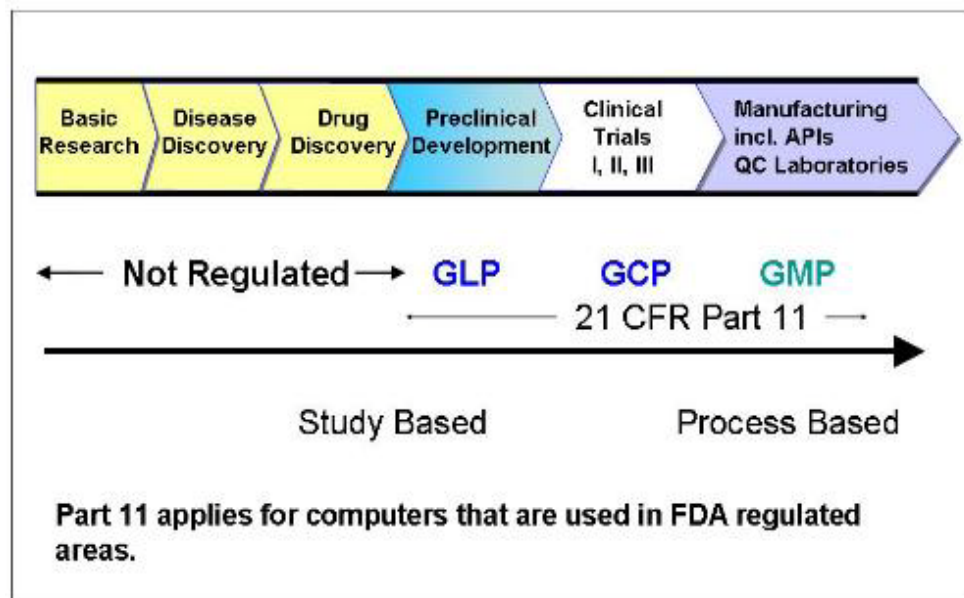


Figure 1. GLP vs. GCP, GMP and 21 CFR Part 11

Typically research and drug discovery are not regulated at all. GLP starts with preclinical development, for example toxicology studies. Clinical trials are regulated by good clinical practice regulations and manufacturing through GMPs. There is a frequent misunderstanding that all laboratory operations are regulated by GLP. This is not true. For example, Quality Control laboratories in manufacturing are regulated by GMPs and not by GLPs. Also Good Laboratory Practice regulations are frequently mixed up with good analytical practice. Applying good analytical practices is important but not sufficient, as we will see in this presentation. When small quantities of active ingredients are prepared in a research or

development laboratory for use in samples for clinical trials or finished drugs, that activity has be covered by GMP and not by GLP.

Part 11 is FDA's regulation on electronic records and signatures and applies for electronic records or to computer systems in all FDA regulated areas. For example, it applies for computers that are used in GLP studies.

Characteristic for GLPs is that they are study based where as GMPs are processed based.

Independent from Location and Duration of a Study

GLPs regulate all non-clinical safety studies that support or are intended to support applications for research or marketing permits for products regulated by the FDA, or by similar other national agencies. This includes drugs for human and animal use but also aroma and color additives in food, biological products and medical devices. The duration and location of the study is of no importance. For example GLP applies to short term experiments as well as to long term studies. And if a pharmaceutical company subcontracts part of a study to a university, that university still must comply with the same requirements as the sponsor company. Some laboratories tried to get away from GLP through outsourcing, but I can tell you this does not work.

GLP is needed for:	GLP is not needed for:
• Non clinical safety studies of development of drugs • Agricultural pesticide development • Development of toxic chemicals • Food control (food additives) • Test of substance with regard to explosive hazards	• Basic research • Studies to develop new analytical methods • Chemical tests used to derive the specifications of a marketed food product

Facility Management and Other Personnel

Qualification of Personnel

Like all regulations also GLPs have chapters on personnel.

The assumption is that in order to conduct GLP studies with the right quality a couple of things are important:* Number one there should be sufficient people and second, the personnel should be qualified.

The FDA is not specific at all what type of qualification or education people should have. Qualification can come from education, experience or additional trainings, but it should be documented. This also requires a good documentation of the job descriptions, the tasks and responsibilities.

Facility management

Responsibilities of facility management are well defined. They include to designate a study director and also to monitor the progress of the study and if it is not going well to replace the study director.

The management is responsible for many things, basically they should assure that a quality assurance unit is available, test and control articles are characterized, and that sufficient qualified personnel is available for the study.

Because it is obvious that management can not take care personally about all this they have to rely on other functions, for example GLPs require that the QA should give a regular report on the compliance status of the study.

Study Director

The position of a study director is unique for GLP. He/she has overall responsibility for the technical conduct of the safety studies, as well as for the interpretation, analysis, documentation and reporting of the results. He or she is designated by and receives support from management. The study director serves as the single point of study control. It is important that this is a single individual person and not a

department or any other grouping of people. An assistant study director is not permitted but there may be an alternate study director who serves as study director only in that person's absence.

The study director may be the laboratory manager and may be responsible for more than one study. However, he or she should not be over-burdened—an auditor could otherwise get the impression that the study director cannot monitor all studies carefully.

xxx See Table from old version!!!

Quality Assurance Unit

The quality assurance unit (QAU) serves an internal control function. It is responsible for monitoring each study to assure management that facilities, equipment, personnel, methods, practices, records, controls, SOPs, final reports (for data integrity), and archives are in conformance with the GLP/GALP regulations. For any given study, the QAU is entirely separate from and independent of the personnel engaged in the direction and conduct of that study.

As well as immediately reporting of any problems, GLP/GALP regulations require the QAU to maintain and periodically submit to laboratory management comprehensive written records listing findings and problems, actions recommended and taken, and scheduled dates for inspection. A designated representative from the FDA or EPA may ask to see the written procedures established for the QAU's inspection and may request the laboratory's management to certify that inspections are being implemented, and followed-up in accordance with the regulations governing the QAU.

Part-time or full-time personnel may be used depending on whether the volume of work is sufficient to justify employing one or more full-time quality assurance professionals. Full-time professionals are the preferred arrangement, because such an arrangement provides a degree of independence and removes the possibility that the demands of the person's second job will interfere with his or her performance of the QA function. For small organizations it might not be possible to designate a full-time person.

The FDA mandates that responsibilities and procedures applicable to the QAU, the records maintained by the QAU, and the method of indexing such records be in writing and be maintained. The agency further requires that these items, including inspection dates, the description of the study inspected, the phase or segment of the study, and the name of the individual performing the inspection, be made available for review by an authorized FDA agent. The FDA agent cannot request the findings of the QAU audit.

Main Responsibilities of the Quality Assurance Unit

Maintain copy of master schedule sheet of all studies conducted. These are to be indexed by test article and must contain the test system, nature of study, date the study was initiated, current status of each study, identity of the sponsor, and name of the study director.

Maintain copies of all protocols pertaining to the studies for which QAU is responsible. Inspect studies at intervals adequate to assure the integrity of the study and maintain written and properly signed records of each periodic inspection. These records must show the date of the inspection, the study inspected, the phase or segment of the study inspected, the person performing the inspection, findings and problems, action recommended and taken to resolve existing problems, and any scheduled date for re-inspection. Any problems discovered which are likely to affect study integrity are to be brought to the attention of the study director and management immediately.

Periodically submit to management and the study director written status reports on each study, noting problems and corrective actions taken. Determine whether deviations from protocols and SOPs were made with proper authorization and documentation.

Review the final study report to assure that it accurately describes the methods and SOPs and that the reported results accurately reflect the raw data of the study. Prepare and sign a statement to be included with the final study report that specifies the dates of audits and dates of reports to management and to the study director. Audit the correctness of the statement, made by the study director, on the GLP compliance of the study.

Facilities

All GLP regulations also have requirements for facilities, for example, animal care facilities are listed as well as animal supply facilities, facilities for handling test and control articles, and laboratories and storage facilities. The main purpose of this is to ensure integrity of the study and of study data. Three main requirements for facilities are

1. Limited access to buildings and rooms
2. Adequate size and
3. Adequate construction.

For example, if a testing facility is too small to handle the specified volume of work there may be a risk to mix incompatible functions. Or if the air conditioning system is wrongly designed, there may be cross contamination between different areas.

Equipment and Computer Systems

All GLP regulations also have requirements for equipment. They are related to design, calibration, maintenance and validation. This includes analytical equipment such as chromatographs, spectrophotometers, and computerized equipment for instrument control and direct data capture, data evaluation, printing, archiving and retrieval. .

Design

Equipment used in generation, measurement, or assessment of data and equipment used for facility environmental control shall be of appropriate design and adequate capacity to function according to the protocol and shall be suitably located for operation, inspection, cleaning, and maintenance. The equipment should undergo a validation process to ensure that it will consistently function as intended. Examples are analytical equipment such as chromatographs, spectrophotometers, computerized equipment for direct data capture, and computers for statistical analysis of data.

Maintenance, calibration, testing and validation

Equipment shall be adequately inspected, cleaned, and maintained. Equipment used for generation, measurement, or assessment of data shall be adequately tested, calibrated and/or standardized. These activities are frequently called qualification for equipment hardware and single modules and validation for software and complete systems. A laboratory shall establish schedules for such operations based on manufacturer's recommendations and laboratory experience.

Time interval for calibration, re-validation and testing

The frequency for calibration, re-validation and testing (performance verification) depends on the instrument itself, the recommendations from manufacturers of equipment, laboratory experience, and the extent of use. For instance, a pH meter should be calibrated before each use and the wavelength of an HPLC variable wavelength detector should be calibrated about every month or whenever the cell is removed and reinstalled. Typically proof of chromatographic instrument performance should be done every 6 to 12 months.

Equipment Records and Other Documents

Written records shall be maintained of all inspection, maintenance, testing, calibrating and/or qualification / validation operations. These records, containing the date of operation, shall describe whether the maintenance operations followed written SOPs. Written records shall be kept of non-routine repairs performed on equipment as a result of failure and malfunction. Such records shall document the nature of the defect, how and when the defect was discovered, and any remedial action taken in response to the defect. Written records may be in log books especially designed for that purpose. A log book should accompany the instrument when it is moved. Remedial action should include a review of effects on data generated before the defect was discovered. Such equipment records should be maintained as long as the data generated by the equipment.

Equipment records should include

- name of the equipment
- name of the manufacturer,
- model or type for identification s
- serial number
- date equipment was received in the laboratory
- condition when received (new, used)
- details of checks made for compliance with relevant calibration or test standard specification
- date equipment was placed in service by the laboratory
- current location in the laboratory, if appropriate
- copy of manufacturer's operating instruction(s)
- details of maintenance carried out
- history of any damage, malfunction, modification or repair
- person responsible for the equipment

Important questions to be answered for any analytical instrument:

For an auditor there are several important questions to be answered for any analytical instrument:

1. What is the equipment being used for and are there specifications?
2. Is the instrument within specification and is the documentation to prove this available?
3. If the instrument is not within specifications, how much does it deviate by?
4. If the instrument is not within specifications, how long has this been the case?
5. If the instrument is not within specifications what action has been taken to overcome the defect?
6. Can the standards used to test and calibrate the instruments be traced back to national standards?

Standard Operating Procedures

Standard operating procedures (SOPs) are written procedures for a laboratories program. They define how to carry out protocol-specified activities. Most often they are written in a chronological listing of action steps.

- Routine inspection, cleaning, maintenance, testing, calibration and standardization of instruments
- Actions to be taken in response to equipment failure
- Analytical methods
- Definition of raw data
- Data handling, storage, and retrieval
- Health and safety precautions
- Receipt, identification, storage, mixing, and method sampling of test and control articles
- Record keeping, reporting, storage, and retrieval of data
- Coding of studies, handling of data, including the use of computerized data systems
- Operation of quality assurance personnel in performing and reporting study audits, inspections, and final study report reviews

SOPs should preferably be written in the laboratory close to the instrument, and not in an office. It should be either written or thoroughly reviewed by the instruments' operators. SOPs should not be written to explain how procedures are supposed to work, but how they work. This ensures that the information is adequate and that the document invites rather than discourages routine use.

Sops are frequently mentioned as deviations in FDA warning letters where three major deviations come up:

- SOPs are not available
- They are not adequate or
- They are not followed.

One of the first procedures should be an SOP on writing SOPs. This is important for consistency and efficiency. For example, it should be defined who is responsible for initiating, authoring, and approving SOPs and how procedures are distributed and how the use of SOPs is enforced. GLPs allow to deviate from SOPs but deviations should be approved and documented.

Reagents and Solutions

To ensure ongoing quality of reagents and solutions used for GLP studies, purchasing and testing should be handled by a quality assurance program. That also should include qualification of suppliers.

All reagents and solutions in the laboratory areas shall be labeled to indicate identity, titer or concentration, storage requirements, and expiration date. Deteriorated or outdated reagents and solutions shall not be used. If reagents and solutions used for non-GLP regulated work are stored in the same room as reagents for GLP-regulated studies, all reagents must be labeled. Reagents that are not adequately labeled, even if not intended for use in GLP-regulated studies, may have an adverse effect on GLP regulated laboratory work. It is also good practice to include the Date opened. This can be critical for some chemicals such as ether.

Many reagents can be stored under ambient temperature: does this mean we have to put a label on all these? One practical recommendation to avoid too much paper work is to have a procedure that has a sentence like this: "You don't need to label environmental conditions on each reagent if it is stored under ambient temperature." So everybody in your lab should know: reagents and solutions without storage temperature do not require cooling for storage

Expiration Date

The expiration date depends on the nature of the chemical. Sodium chloride has practically no expiration date. In these cases it might be acceptable to indicate NONE or Not applicable (N/A) on the label for expiration date. The laboratory must be prepared to justify this designation. Formal studies are not always required to justify assigned expiration dates. It is sufficient to assign expiration dates based on literature references and/or laboratory experience.

Test and Control Articles

Control articles or reference substances as they are called in the OECD principles are of utmost importance because they are commonly used to calibrate the instrument. The accuracy of the reference substances also determines the accuracy of the analytical method. In other words, if the reference standard is wrong, also the test result.

Main requirements for control articles are: The identity, strength, purity, composition and other characteristics should be determined for each batch and documented. * Methods of synthesis, fabrication, or derivation of test and control articles should also be documented. Copies of this documentation must be stored with the study data and must be available for FDA inspection.

In addition, the stability of each test or control article should be determined. This can be done either before study initiation, or simultaneously according to written SOPs which provide for periodic reanalysis of each batch.

Each storage container for a test or control article should be labeled by name, chemical abstract number or code number, batch number, expiration date, and, where appropriate, storage conditions necessary to maintain the identity, strength, purity and composition.

Furthermore, storage containers should be assigned to a particular test article for the length of the study. Certified reference standards can be purchased from appropriate suppliers. If standards are not available, the recommendation is to take a lot of your own material, and analyze, certify and use it as the standard. However, they should be made from high purity material and be compared against the primary standard to ensure the traceability chain. For the comparison, validated test methods should be used.

Conduct of a Study, Study Protocol and Study Report

Study Protocol

Each GLP study should be conducted according to a study protocol. The study director writes the study protocol to document what should be done and when, it also describes anticipated exceptions from SOPs. Most important is the description of the experimental design and the type and frequency of tests and analyses. The study protocol also documents which records should be archived and available for inspections.

As a minimum the study protocol should include:

- Title and statement of the purpose of the study
- Identification of test and control article *
- Identification of test system
- Name of the sponsor,
- Description of experimental design,
- Type and frequency of tests and analyses
- Records to be maintained

Conduct of a Study

The study should follow strictly the protocol and any deviations should be documented, if there are any. This section also includes requirements on how hand-recorded data and data captured from automated equipment should be recorded. For example, hand written data must be recorded in ink and not with a pencil. Changes must not obscure the original entry but must be dated and signed together with a reason for the change. When data are acquired from an automated system, the person responsible for the system and the system itself should be identified and documented.

Records

GLP regulations specify what should be recorded. Examples include

- Name and address of the laboratory
- Objectives and procedures
- Statistical methods
- Test and control articles, incl. stability data
- Description of methods
- Description of test system
- Description of dosage, route of administration, duration
- Name of the study director
- Location where raw specimens and data are stored
- Descriptions of transformations and calculations

Most of requirements are quite obvious, but let's look at the last bullet:. GLP inspectors want to see on how final results have been derived from raw data. This means to document it on paper when you use a calculator, it also can mean to store the formulas as part of an Excel spreadsheet, or for commercial systems formulas are included in the operation manual. Sometimes software companies don't disclose calculations used in their software to protect intellectual proprietary. This usually did not appear to be a big problem as long as you document it.

Retention and Retrieval of Records

GLPs have several paragraphs with details on how to store and retrieve records and data, for example, what should be archived and retention time.

What should be archived

The list of documents that should be archived includes everything from raw data to final results, but also protocols from meetings, if decisions related to the integrity of a study have been made.

GLPs require the position of an archivist. This is either a part time or full time person who is responsible for the archive. Some companies have a procedure that requires documents from an archive to only be checked out by the archivist or his designate. Whenever documents are taken out of the archive this should be documented, and the person who requests it should sign a statement that nothing has been changed, added or deleted.

Retention Periods

GLPs also specify for how long records and specimens should be retained. For example, in the US material supporting FDA submissions should be retained until

- 2 years after FDA approval or
- 5 years after FDA submission

For wet specimens may be shorter: they should only be retained as long as the quality affords evaluation. However, this is only for US FDA and retention times in other countries may be different.

The numbers such as 2 and 5 years don't look as a long time. However, two years after FDA approval and 5 years after an FDA submission can be a long time. Sometimes it may take ten or more years between the time GLP studies have been conducted and approved by the FDA.

GLP says you can keep either the original or an exact copy of a record. An exact copy can be a copy of an unstable thermo paper to durable plain paper or when paper records are scanned into TIF or PDF files.

Responsibility for Archiving

The sponsor company is responsible for the records. When a sponsor company out-sources studies or also just the archiving part, the sponsor company must make sure that archiving of records complies with GLP regulations and in case the contractor goes out of business the sponsor company has access to all data. Long archiving time as required by GLP typically is no problem for normal paper records, but it may be one for electronic records, especially when records are archived as original records in the proprietary applications format. Examples are chromatographic or spectroscopic data. So the question is always whether electronic records can be printed and the original records can be deleted. For this discussion we take a closer look into the definition of raw data.

Raw Data

GLPs also have specific requirements for raw data. They are defined as any laboratory worksheets, records, memoranda, notes, or exact copies thereof, that are the results of original observations and activities of a study. The term covers all data necessary for the reconstruction of the report of the study. Raw data may include hand-written notes, photographs, microfiche copies, computer print-outs, magnetic media, dictated observations, and recorded data from automated instruments.

Examples also include records of animal receipt, results of environmental monitoring, instrument calibration records, and integrator output from analytical equipment. Raw data may also be entries in a worksheet used to read and note information from an LED display of an analytical instrument.

Electronic Records

Raw data are well defined as long as information is recorded on paper. For example original observations are recorded on paper and exact copies can be made if necessary. A more frequently discussed question is what is an exact copy of a paper print-out that comes from an electronic record. Most important here is to look again at the definition of an exact copy: as long as the print-out includes everything that is necessary to reconstruct the study, there should not be a problem. Or as an FDA professional explained to a conference audience: as long as you can demonstrate compliance with the regulation. For example, one requirement of GLP is to document in an audit trail when data have been changed. So look if the print-out includes the audit trail information, for example when data on the computer have been changed. An other question would be if all chromatographic peak in the print-out are on scale?

GLP Inspections and Enforcement

It is FDA's responsibility to enforce the federal Food, drug and Cosmetic Act to ensure safety and effectiveness of drugs and medical devices. This is enforced through regulations, guidance documents and FDA inspections. The FDA has the responsibility to inspect GLP studies related to products that are marketed in the United States, it does not matter where the products are developed or manufactured.

Inspection Program

The FDA has developed an inspection program with two types of inspections: Routine inspections and 'For cause' inspections. Routine inspections should be conducted at least every second year. It is an on-going evaluation of a laboratory's compliance with GLP regulation.

For cause inspections are less frequent, they constitute only about 20% of all GLP inspections. Reasons for such inspections could be a follow up of an inspection with serious deficiencies or when the FDA suspect non-compliance when investigating NDA applications. It also may happen that the FDA gets some hints from external sources about non-compliance in laboratories.

Typically the FDA does not announce GLP inspections. If a laboratory refuses to accept FDA inspections, either in full or also part of it, the FDA will not accept studies in support of new drug applications.

Enforcement

Deviations from GLP requirements are documented in different ways: if the inspection team finds deviations, they write them in a specific form which has the number 483. The deviations are discussed during the exit meeting and the laboratory can respond. Then the lead inspector writes a full inspection report which is called: establishment inspection report. This may be up to 20 or 30 pages. Depending on the deviations the inspector will or will not write a warning letter. This letter is sent to the company's management. Within 14 days the company should respond with a corrective action plan.

Links to Other Websites

[Links to international GLP regulations and guidelines](#)

[Links to FDA regulations](#)

Expert Advice on Selected Topics

Not yet available

Questions and Answers

Not yet available

Quality System Regulation 21 CFR 820 Basic Introduction

Kimberly A. Trautman
FDA's Medical Device Quality Systems Expert

Overview

- Background
- Definitions
- Subsystems
 - Management
 - Design and Development Controls
 - Production and Process Controls
 - Corrective and Preventive Actions
- Resources

2

Background

Effective June 1, 1997, replacing the 1978 GMP for medical devices
Preamble to the 1997 regulation - VERY Important
Requirements are not prescriptive
Provides framework of basic requirements for manufacturers to follow

3

Quality Management System

A manufacturer must develop a Quality Management System (QMS) commensurate with:

- risk presented by the device
- complexity of device and manufacturing processes
- size and complexity of organization

4

Quality System Regulation

820.3 Definitions

Establish means define, document (in writing or electronically), and implement.

5

Quality System Regulation

820.3 Definitions

Finished device means any device or accessory to any device that is suitable for use or capable of functioning, whether or not it is packaged, labeled, or sterilized.

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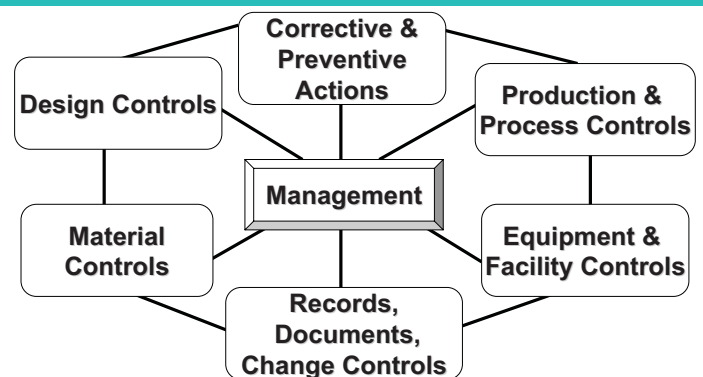
Quality System Regulation

820.3 Definitions

Manufacturer means any person who designs, manufactures, fabricates, assembles, or processes a finished device. Manufacturer includes but is not limited to those who perform the functions of contract sterilization, installation, relabeling, remanufacturing, repacking, or specification development, and initial distributors of foreign entities performing these functions.

7

Quality Management Subsystems



8

Management Subsystem

820.20 Management Responsibility
820.22 Quality Audits
820.25 Training

9

820.20 Management Responsibility

Quality Policy.

- Must be established by management with executive responsibility.
- Must be understood, implemented, and maintained at all levels of the organization.

10

820.20 Management Responsibility

Must establish and maintain an adequate organizational structure, including

- Appropriate responsibility, authority, and interrelation of personnel
- Adequate resources
- Appointed management representative

11

820.20 Management Responsibility

Management Review

Management with executive responsibility shall review the suitability and effectiveness of the quality system

- At defined intervals
- With sufficient frequency
- According to established procedures

12

820.20 Management Responsibility

Management Representative

- Member of management.
- Responsible for ensuring establishment of quality system and reporting on quality system performance to management with executive responsibility.

13

820.22 Quality Audit

- Establish procedures for quality audits.
- Conduct audits to assure compliance by individuals not having direct responsibility for areas audited.

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820.22 Quality Audit

- Perform corrective action(s), including reaudit of deficiencies.
- Generate a written report of audit results for management review.

15

820.25 Personnel

- Hire sufficient personnel with necessary education, background, training, and experience.
- Establish procedures for identifying training needs and to ensure personnel are adequately trained.
- Document training.

16

820.25 Personnel

- Make personnel aware of device defects that could occur from improper job performance.
- Make personnel aware of defects and errors that could be encountered as part of their job.

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Design and Development Subsystem

- 820.30 Design Controls
- 820.70(b) Production and Process Changes
- 820.181 Device Master Record
- 820.250 Statistical Techniques

18

820.30 Design Controls

- Since 1984, the FDA has identified lack of design controls as one of the major causes of device recalls.
- The SMDA provided the FDA with the authority to add preproduction design controls to the device GMP regulation.

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820.30 Design Controls

- The design control requirements are not intended to apply to development of concepts and feasibility studies.

Preamble #62

- FDA will evaluate the process, the methods, and the procedures that a manufacturer has established to implement the requirements for design controls.

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820.30 Design Controls

- The FDA has amended the IDE regulation, reaffirming that an IDE device is exempted from complying with the GMP's ... with the exception of Sec. 820.30 "Design Controls."
- FDA will not inspect design controls during bioresearch monitoring inspections.

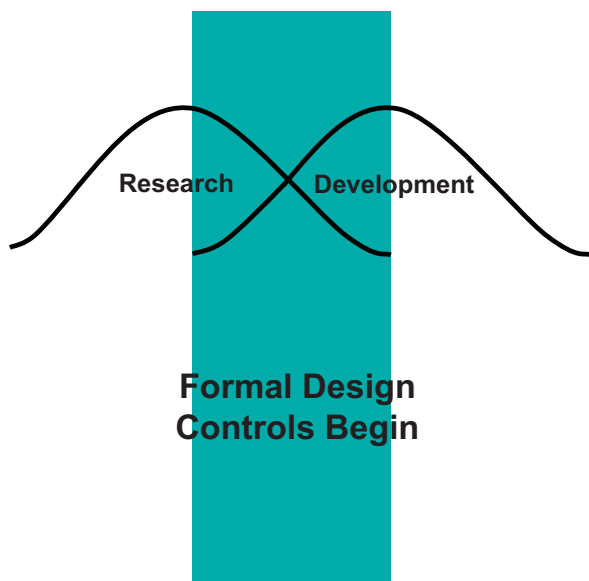
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820.30 Design Controls

Applicable to all class II and III and the following class I devices

- Devices automated with computer software
- Tracheobronchial suction catheters
- Surgeon's gloves
- Protective restraints
- System, radionuclide applicator, manual
- Source, radionuclide teletherapy

22



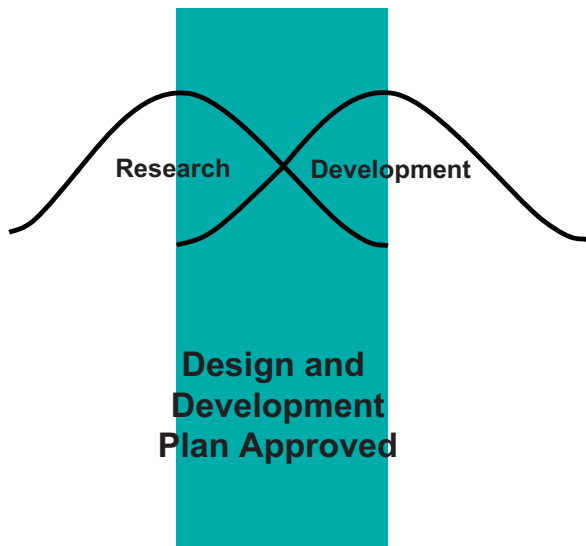
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Design and Development Planning

Describe design and development activities.

- Define responsibility for implementation.
- Identify and describe interfaces between different groups or activities.
- Review, update, and approve plans as design and development evolves.

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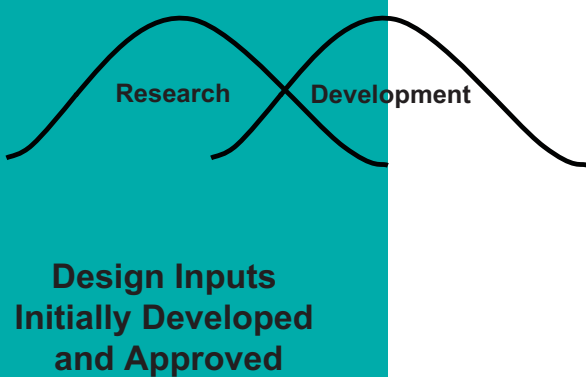


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Design Input

- Ensure requirements are appropriate and address intended use of device.
- Address incomplete, ambiguous, or conflicting requirements.
- Document, review, and approve input requirements.

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Design Output

- Define and document design output in terms that allow evaluation to design input.
- Reference acceptance criteria.
- Identify design outputs essential for the proper functioning of device.
- Document, review, and approve design outputs before release.

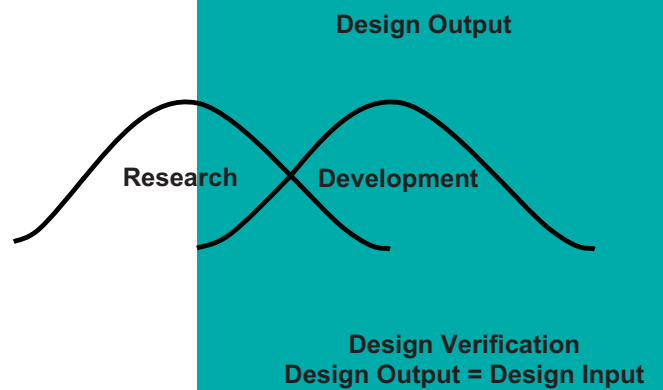
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Design Output

Design output.

- Results of design effort at each phase and the end of the total design effort.
- Finished design output is basis for the DMR.

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Design Review

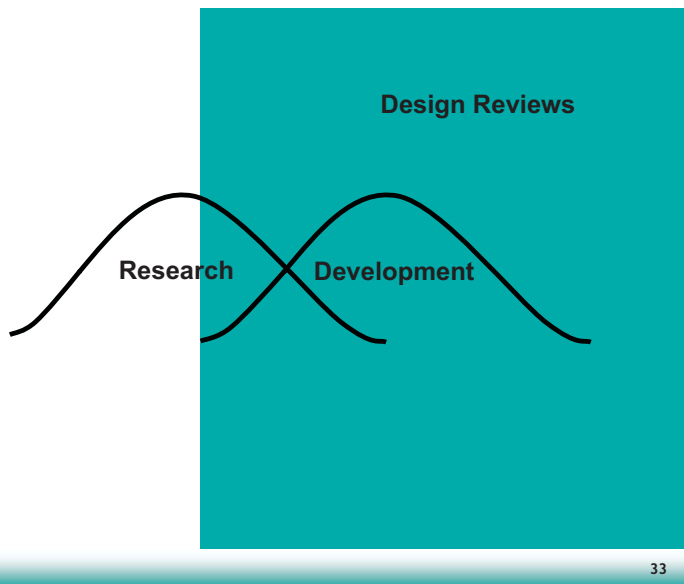
- A documented, comprehensive, systematic examination to
 - Evaluate adequacy of the design requirements
 - Evaluate capability of the design to meet requirements
 - Identify problems
- Ensure that formal reviews of design results are planned and conducted at appropriate stages.

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Design Review

- Ensure participants include representatives of all functions concerned with design stage being reviewed.
- Document results in the Design History File (DHF).

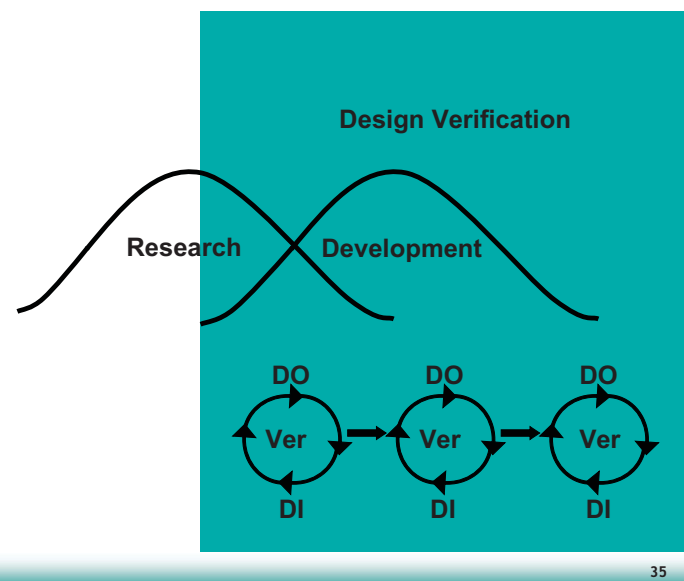
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Design Verification

- Verify the device design.
- Confirm that design output meets design input requirements.
- Document results in the DHF.

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Design Validation

820.3 Definitions – Design Validation

Design validation means establishing by objective evidence that device specifications conform with user needs and intended use(s).

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Design Validation

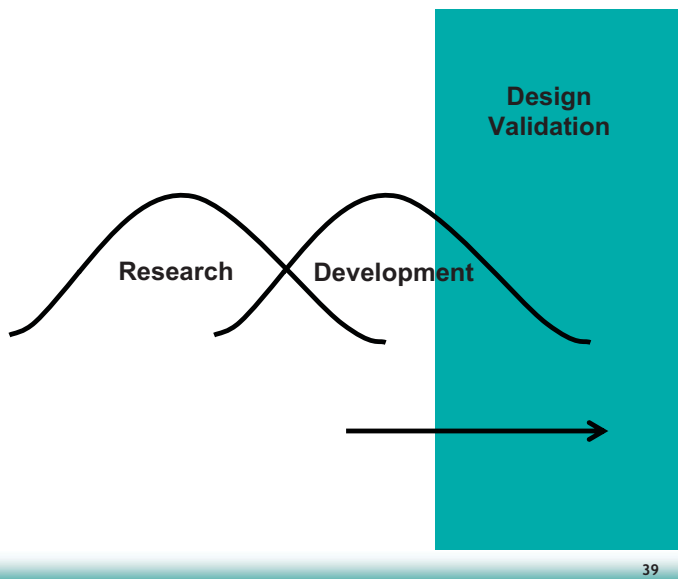
- Validate the device design.
- Perform under defined operating conditions on initial production units or equivalent.
- Ensure devices conform to defined user needs and intended uses.

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Design Validation

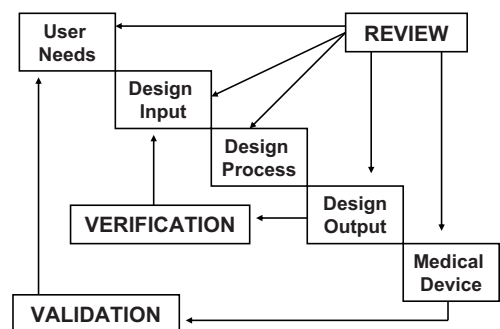
- Test of production units under actual or simulated use conditions.
- Perform software validation and risk analysis, where appropriate.
- Document results in the DHF.

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Design and Development



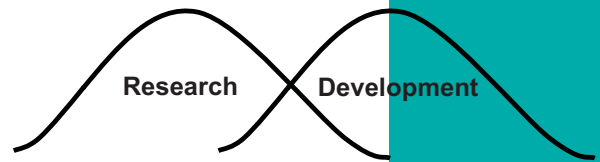
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Design Transfer

- Ensure the device design is correctly translated into production specifications.

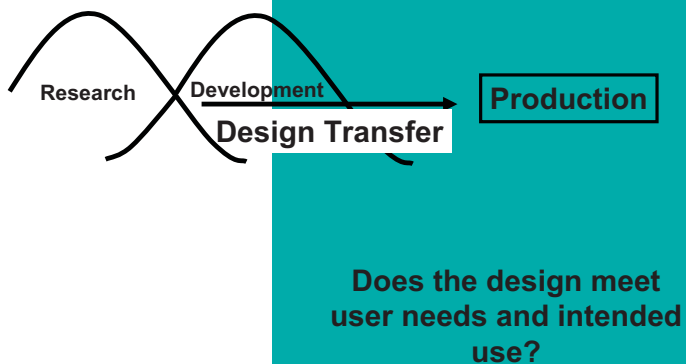
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Design Transfer



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Design Validation

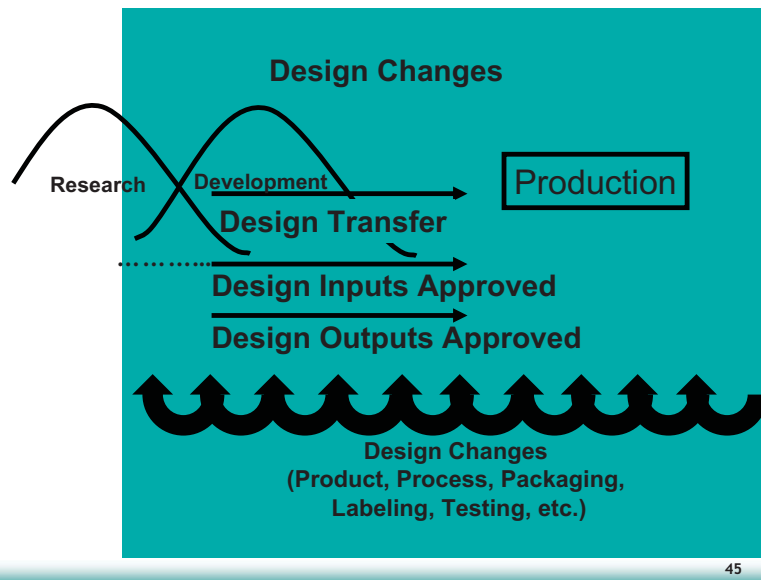


43

Design Changes

- Identify, document, validate or verify, review, and approve design changes before implementation.

44



Design History File

820.3 Definitions – Design History File

Design history file (DHF) means a compilation of records which describes the design history of a finished device.

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Design History File

- Establish and maintain a DHF for each type of device.
- Maintain records to demonstrate development was in accordance with design plan and requirements of 820.30.
- Forms the Device Master Record (DMR)

47

Production and Process Controls Subsystem

- 820.50 Purchasing Controls
- 820.60 Identification
- 820.65 Traceability
- 820.70 Production and Process Controls
- 820.72 Inspection, measuring, and test equipment
- 820.75 Process Validation

48

Production and Process Controls Subsystem

- 820.80 Receiving, in-process, and finished device acceptance
- 820.86 Acceptance Status
- 820.120 Device labeling
- 820.140 Handling
- 820.150 Storage
- 820.160 Distribution
- 820.170 Installation

49

820.50 Purchasing Controls

Establish and maintain procedures to ensure that all purchased or otherwise received product and services conform to specified requirements

Evaluate suppliers, contractors and consultants

50

820.50 Purchasing Controls

Establish and maintain purchasing data/documents that describe or reference specified requirements (including notification of change agreements)

Approve purchasing data/documents

51

820.50 Purchasing Controls

GHTF Guidance Document:

“Quality management system-Medical Devices-Guidance on the control of products and services obtained from suppliers”

52

820.50 Purchasing Controls

A supplier is anyone that is independent from the manufacturer's quality management system and not apart of their Quality Audit.

- Internal Supplier
- External Supplier

53

820.50 Purchasing Controls

An internal supplier:

- Part of the manufacturer's organization
- Operates under a separate quality management system
- Not part of the manufacturer's internal audit scope (quality audit)

54

820.50 Purchasing Controls

Internal suppliers are to be controlled in a similar way as external suppliers

Both internal and external suppliers are required to be controlled under 21 CFR 820.50.

55

820.70 Production and Process Controls

Develop, conduct, control, and monitor production processes to ensure devices conform to specifications.

56

820.70 Production and Process Controls

Production and process changes.

- Establish procedures for changes to a specification, method, process, or procedure according to §820.30 Design Controls
- Verify/ validate according to §820.75.
- Approve in accordance with §820.40.

57

820.70 Production and Process Controls

Environmental control.

- Establish procedures to adequately control environmental conditions.
- Inspect control system(s) to verify adequacy and proper functioning.
- Document and review these activities.

58

820.70 Production and Process Controls

Automated processes.

- Validate computer software used as part of production or the quality system for its intended use.
- Validate according to an established protocol.
- Validate all software changes before approval.
- Document validation activities and results.

59

820.75 Process Validation

Process validation means establishing by objective evidence that a process consistently produces a result or product meeting its predetermined specifications.

60

820.75 Process Validation

Process Validation

- Where the results of a process cannot be fully verified by subsequent inspection and test, the process shall be validated with a high degree of assurance and approved according to established procedures.

61

820.75 Process Validation

Control of Validated Processes.

- Monitoring and control methods and data
- Date performed
- Individual(s) performing the process, where appropriate
- Major equipment used, where appropriate

62

820.75 Process Validation

Revalidation.

- When changes or process deviations occur, the manufacturer shall review and evaluate the process and perform revalidation where appropriate.

63

820.80 Receiving, In-Process, & Finished Device Acceptance

Receiving acceptance activities.

- Establish procedures for acceptance
- Inspect, test, or otherwise verify as conforming
- Document acceptance or rejection

64

820.80 Receiving, In-Process, & Finished Device Acceptance

In-process acceptance activities.

- Establish acceptance procedures to ensure specified product requirements are met.
- Control in-process product until appropriate acceptance activities are completed and documented.

65

820.80 Receiving, In-Process, & Finished Device Acceptance

Final acceptance activities.

- Establish and maintain procedures for finished device acceptance to ensure each production run, lot, or batch meets acceptance criteria.
- Control finished devices until appropriate activities required for release are completed.

66

Corrective and Preventive Actions (CAPA) Subsystem

- 820.100 CAPA
- 820.90 Nonconforming Product
- 820.198 Complaints
- 820.200 Servicing
- 820.250 Statistical Techniques

67

820.100 Corrective and Preventive Action

- Collect and analyze data to identify nonconforming product and other quality problems
- Investigate cause
- Identify and implement corrective and preventive action

68

820.100 Corrective and Preventive Action

- Verify and validate actions and effectiveness
- Communicate information on the quality problems and the necessary actions to appropriate staff
- Forward information to management review

69

Correction vs. Corrective Action

“Correction” refers to repair, rework, or adjustment and relates to the disposition of an **existing** nonconformity

“Corrective action” relates to the elimination of the **causes** of an existing nonconformity

70

“Healthy” CAPA subsystem procedures include provisions to

1. Identify and correct existing nonconforming product or other quality problems (“Correction”);
2. Identify and eliminate the causes of existing nonconforming product and other quality problems (“Corrective Action”); and,

71

“Healthy” CAPA subsystem procedures include provisions to

3. Identify and eliminate the causes of potential nonconforming product and other quality problems (“Preventive Action”)

72

820.90 Non-Conforming Product

- Establish and maintain procedures, including
 - Identification
 - Documentation
 - Evaluation
 - Segregation
 - Disposition
- Document the evaluation and any investigation

73

820.90 Non-Conforming Product

Nonconformity review and disposition.

- Establish and maintain procedures defining the responsibility for review and the authority for the disposition, including the review and disposition process.
- Document disposition of nonconforming product, including the justification for use and the signature of individual(s) authorizing use.

74

820.90 Non-Conforming Product

Nonconformity review and disposition.

- Establish and maintain procedures for rework, including retesting and reevaluation.
- Document rework and reevaluation activities in the DHR.

75

820.198 Complaint Files

All manufacturers must

- Maintain complaint files.
- Designate a formal complaint handling unit.
- Establish and maintain procedures for receiving, reviewing, and evaluating complaints.

76

820.198 Complaint Files

Procedures must ensure that

- All complaints are processed in a uniform and timely manner.
- Oral complaints are documented upon receipt.
- Complaints are evaluated to determine whether the complaint represents an Medical Device Report.

77

820.198 Complaint Files

Investigations.

- Review and evaluate all complaints to determine whether an investigation is necessary.
- Records of investigation shall be maintain with certain specified information as required

78

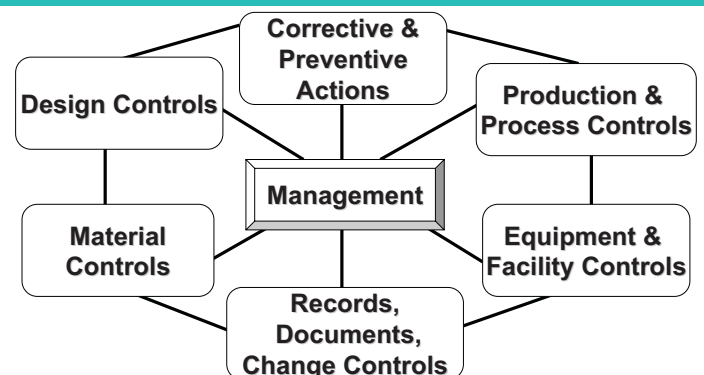
820.198 Complaint Files

Investigations.

- When no investigation is made, maintain a record that includes the
 - Reason no investigation was made and name of the individual responsible for the decision.

79

Quality Management Subsystems



80

Close the loop...



Additional Resources

- FDA Compliance Program 7382.845
Inspection of Medical Device Manufacturers
implemented October 1, 2000
www.fda.gov/ora/cpgm/default.htm#devices
- Guide to Inspections of Quality Systems,
August 1999
www.fda.gov/ora/inspect_ref/igs/qsit/qsitguide.htm

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Additional Resources

“Quality System Information for Certain
Premarket Application Reviews:
Guidance for Industry and FDA Staff”:
2003

[http://www.fda.gov/cdrh/comp/guidance/
1140.pdf](http://www.fda.gov/cdrh/comp/guidance/1140.pdf)

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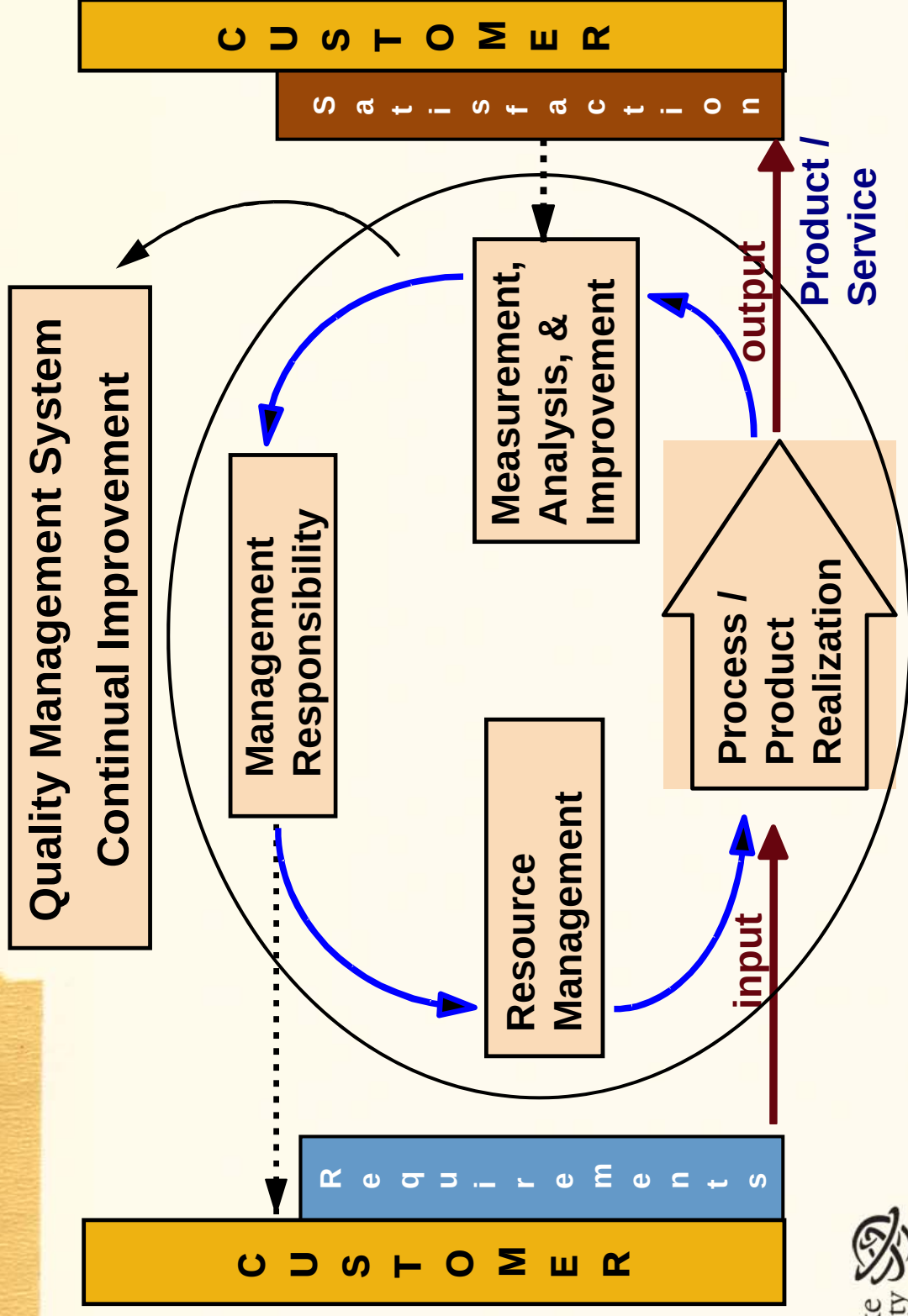
Additional Resources

Global Harmonization Task Force Quality
Management System Guidance Documents
<http://www.ghtf.org/sg3/sg3-final.html>

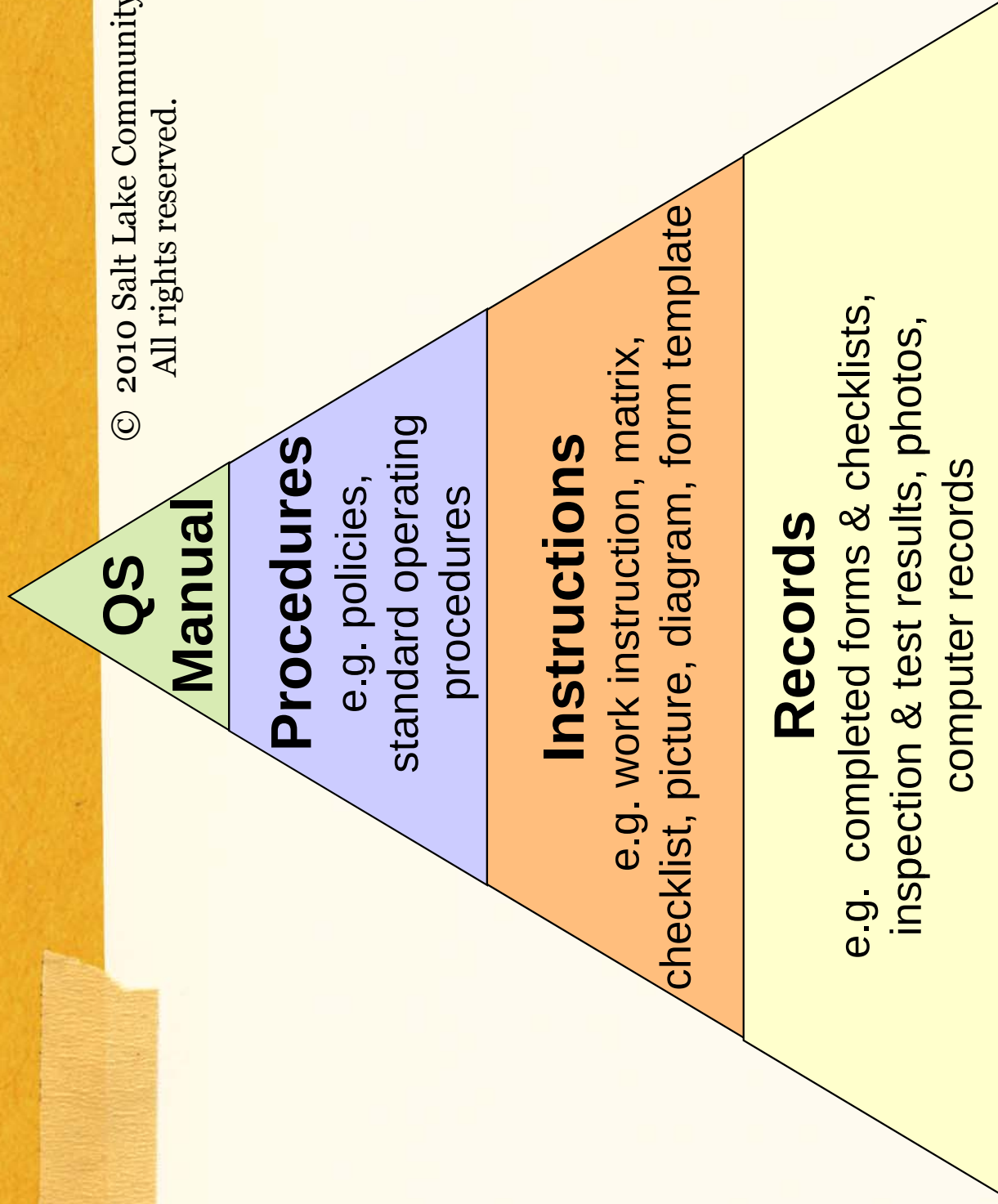
- “Implementation of Risk Management
Principles and Activities Within a Quality
Management System”: GHTF 2005
- “Quality Management Systems - Process
Validation Guidance”: GHTF 2004

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QMS PROCESS MODEL



QMS DOCUMENTS



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Home

Self Assessment

This self assessment will help you find where you can make your best contribution to the Innovation process. Knowing your best role will enable you to make your most valuable contribution. You will find out whether you are a Creator, a Connector, a Developer or a Doer. Understanding your role and those of other people you work with will enable you to work more effectively with your colleagues. **(Tell your friends about this self assessment)**

There are twelve questions with four choice answers to each and they will probably take you about ten minutes to answer. Have fun!

- Go to the first line and decide which phrase most describes you – score 4 pts.
- Then decide which phrase is least like you and score 1 pt.
- There are two phrases remaining score 3 pts for the phrase more like you and 2 pts for the phrase less like you
- Continue down each line until you have completed all ten lines
- You must have a '4' a '3' a '2' and a '1' on each line
- When you have finished you will be told which is your best role in the Innovation process and also the primary task for that role.

1.	☐ I must understand an issue	☐ I make things work	☐ I see both sides of an issue	☐ There is a right answer
2.	☐ Don't tell me what to do	☐ Give me facts not theory	☐ I create choices	☐ I like to analyze data
3.	☐ I am open minded	☐ I convince people	☐ I have lots of ideas	☐ I find a weakness
4.	☐ I 'Connect the Dots'	☐ I get things done	☐ I like Possibilities	☐ I bring things 'down to earth'
5.	☐ A Concept must be sound	☐ I like 'energy'	☐ I Don't fuss with details	☐ I like precision
6.	☐ I do not like confusion	☐ I avoid theory	☐ I avoid decisions	☐ I do not like failure
7.	☐ I think things through	☐ I take risks	☐ I like to hear about problems	☐ I focus
8.	☐ I want to own the problem	☐ I find a way that works	☐ I like the big picture	☐ I am thorough
9.	☐ I like to define the problem	☐ I want agreement	☐ I find out the facts	☐ I Plan
10.	☐ I want ideas	☐ I want to try new things	☐ I want Space	☐ I want structure



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Home

Self Assessment

0 Connector 0 Doer 0 Creator 0 Developer

Your Highest Score tells you your best role

The 'Connectors' are the 'Green Thumb' who nurture the Seed of the idea and find the Answer. They are the Design, R & D and Strategic Planning people.

The Doers finally take it to market and Get the job finished. They are Project Managers, Salespeople or folks from Production. Like the Gold Diggers they are Practical People

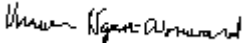
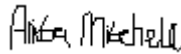
The Creators typically find the opportunity and open it up. If you do this you are likely to be an Artist, Marketeer or Researcher.

The Developers also learn by Thinking but make the idea work. They are Engineers, Systems Developers and Accountants.

If you would like to obtain a detailed description of your type of innovator please [click here](#).

Tell a friend about this self assessment [click here](#)

WID – 1120.001 : Preparation of 0.5 M Tris, pH 7.8

Approvals:	Name	Date	Signature
Author	Vivian Ngan-Winward	2010-02-26	
Reviewer	Anita Mitchell	2010-02-26	

Document History:

Revision Number	Date	Purpose	Effector
1	2010-02-26	Initial release	Vivian Ngan-Winward

1. Purpose:

- 1.1. To prepare 250 mL of 0.5 M Tris solution at pH 7.8

2. Scope:

- 2.1. This procedure should be followed by all technicians preparing 0.5 M Tris solution at pH 7.8, using a calibrated Accumet AB15E pH meter.

3. Responsibilities:

- 3.1. Technicians using this procedure must be adequately trained on the use of the Accumet AB15E pH meter.
- 3.2. Technicians using this procedure are responsible for following the set safety procedures for the facility.
- 3.3. Technicians using this procedure are responsible for following appropriate documentation policies.

4. References:

- 4.1. Accumet AB15E pH meter instruction manual.
- 4.2. WID-XXXX.1 Use of Accumet AB15E pH meter
- 4.3. SOP-BBBB.1 Facility Rules and Regulations
- 4.4. SOP-DDDD.1 Proper Documentation Procedures

5. Definitions:

- 5.1. “**Buffer**” refers to Tris buffer.
- 5.2. “**Meter**” refers to accumet pH meter
- 5.3. “**std**” refers to standardize / standardize button
- 5.4. Temperature shall be indicated in the Celsius scale
- 5.5. “**Good electrode**” refers to range of 90 – 102 % for the slope calculation.
- 5.6. “**Electrode error**” refers to standardization attempt falling outside the acceptable range for the slope calculation.
- 5.7. “**stable**” refers to a pH measurement that has stabilized

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5.8. “**Electrode**” and “**probe**” can be used interchangeably.

6. Precautions:

- 6.1. Take care not to damage the **glass bulb** at the bottom tip of the electrode.
- 6.2. The electrode must always be kept immersed in solution, not left exposed to air.
- 6.3. Prior to use of the pH meter, ensure that the electrode is filled appropriately with electrode storage solution.
- 6.4. When in use, the electrode vent must be open for accurate readings.
- 6.5. Calibration of the meter should be performed immediately before it is used to measure the pH of the Tris solution being prepared.

7. Equipment and Materials:

- 7.1. Accumet AB15E pH meter
- 7.2. Transfer pipet
- 7.3. Magnetic stir plate
- 7.4. Beaker
- 7.5. 2 Stir bars
- 7.6. Set of pH buffer standards: 4.0, 7.0, and 10.0
- 7.7. Top loading balance
- 7.8. Tris base
- 7.9. Weigh boats
- 7.10. 6.0 M HCl
- 7.11. Distilled water
- 7.12. Waste bucket
- 7.13. Buffer sample cups
- 7.14. Non-latex gloves (various sizes)
- 7.15. Safety glasses
- 7.16. Graduated cylinder
- 7.17. Pipets and pipet bulb

8. Procedure:

- 8.1. Use this WID in conjunction with BATCH RECORD-1120.001. Record lot numbers for all materials used.
- 8.2. Standardize Accumet AB15E pH meter as follows:
 - 8.2.1. Set up pH meter (plug in, power up).
 - 8.2.2. Open vent hole at top of electrode.
 - 8.2.3. Set pH meter mode to “pH”.
 - 8.2.4. Pour pH standards (4.0, 7.0, and 10.0) into separate sample cups.
 - 8.2.5. Press “Setup” button twice and “Enter” button once to clear previous standardization.
 - 8.2.6. Remove bottle containing electrode storage solution from tip of electrode.
 - 8.2.7. Rinse tip of electrode with Nanopure water; shake off excess rinse water.

WID – 1120.001 : Preparation of 0.5 M Tris, pH 7.8

- 8.2.8. Place electrode into pH standard 7.0.
- 8.2.9. Press “std” button.
- 8.2.10. Wait until pH reading has stabilized.
- 8.2.11. Press “std” button to lock in reading.
- 8.2.12. Repeat steps 8.2.7 to 8.2.11 with pH standard 10.0.
- 8.2.13. Repeat steps 8.2.7 to 8.2.11 with pH standard 4.0.
- 8.2.14. If standardization procedure is successful, “Good Electrode” message will appear on bottom of screen.
- 8.2.15. If “Electrode Error” message appears, start over from step 8.2.5.
- 8.3. Weigh out $15.1 \text{ g} \pm 0.15 \text{ g}$ Tris base.
- 8.4. Pour Tris base into beaker.
- 8.5. Place a magnetic stir bar into beaker.
- 8.6. Measure 210 mL Nanopure water.
- 8.7. Pour Nanopure water into beaker with Tris base.
- 8.8. Using magnetic stir plate, mix solution at medium speed until Tris base is dissolved.
- 8.9. Rinse tip of electrode with Nanopure water; shake off excess rinse water.
- 8.10. Place electrode into Tris base solution so that at least the top of the silicon plug inside the electrode is submerged, and the electrode tip is off to one side of the beaker.
- 8.11. Allow the pH reading to stabilize.
- 8.12. Take note of the pH reading – it should be above 7.8.
- 8.13. Obtain 20 mL of HCl.
- 8.14. Add HCl 1 mL at a time, allowing the pH reading to stabilize in between additions, until the pH reaches 8.0
- 8.15. Add HCl 10 drops at a time, allowing the pH reading to stabilize in between additions, until the desired pH of 7.8 is reached.
- 8.16. Pour Tris solution into a 250 mL graduated cylinder.
- 8.17. Add Nanopure water to obtain a total volume of $250 \text{ mL} \pm 3 \text{ mL}$.
- 8.18. Pour Tris solution back into beaker.
- 8.19. Check pH of Tris solution to ensure that it is still 7.8. If not, add HCl by drops until the pH is stable at 7.8.
- 8.20. Measure remaining volume of HCl. Subtract this volume from 20 mL (the starting volume).
- 8.21. Record the volume of HCl added.
- 8.22. Prepare the pH meter for storage as per meter manufacturer’s instructions.

9. Attachments: n/a

BATCH RECORD – 1120.001 : Preparation of 0.5 M Tris, pH 7.8

Approvals:	Name	Date	Signature
Author	Vivian Ngan-Winward	2010-02-26	<i>Vivian Ngan-Winward</i>
Reviewer	Anita Mitchell	2010-02-26	<i>Anita Mitchell</i>

Document History:

Revision Number	Date	Purpose	Effector
1	2010-02-26	Initial release	Vivian Ngan-Winward

Materials	Lot Number	Amount Added	Technician Initials
pH 4.0 Standard		n/a	
pH 7.0 Standard		n/a	
pH 10.0 Standard		n/a	
Tris base			
HCl, 6 M			
Measurements of Record		Value	Technician Initials
Final pH of solution			
Final temperature of solution			

Comments

Batch ID	Technician Name	Technician Signature	Date

Appendix I

Glossary

Lean production constitutes a language, much of which is Japanese. In my work, I have found a fairly even split between people who like the Japanese terms and others who prefer their English equivalents. I have developed the following glossary to accommodate both groups.

Japanese words tend to be visual and metaphorical. Often there are no English equivalents. I have tried to provide the nearest equivalent English term, as well as, the most vivid metaphor to convey the meaning as closely as possible.

4 Ms: Man/woman, machine, material, and method.

Affinity diagram: A tool for gathering and grouping ideas; one of the new seven quality tools; used in hoshin planning.

Andon: A line stop; typically a cord that a worker can pull to stop the assembly line when he or she detects a defect; an example of jidoka.

Cell: An arrangement of people, machines, materials, and methods such that processing steps are adjacent and in sequential order so that parts can be processed one at a time (or in some cases in a consistent small batch that is maintained through the process sequence). The purpose of a cell is to achieve and maintain efficient continuous flow.

Continuous flow: In its purest form continuous flow means that items are processed and moved directly to the next process one piece at a time. Each processing step completes its work just before the next process needs the item, and the transfer batch size is one. Also known as one-piece flow and “make one, move one.”

Deshi: Student.

Dojo: Training hall.

Fishbone diagram: A problem-solving and brainstorming tool; also known as a Cause and Effect diagram; one of the Seven Quality Tools.

From: Lean Production Simplified, Appendix 63
2nd edition, Pascal Dennis (2007)

Five S: A system of workplace standardization and organization. The five Ss are sort, set in order, shine, standardize, and sustain.

Five Why Analysis: A problem-solving technique that entails continually asking why until the root cause is found.

Gemba: The real place or the specific place. Usually means the shop floor and other areas where work is done.

Genchi genbutsu: Go see; go to the real place and see what is actually happening.

GTS: Grasp the situation; the heart of PDCA.

Hansei: Reflection; part of both hoshin planning and problem solving.

Heijunka: Production leveling.

Hoshin: A statement of objectives, goals, direction, and/or policy.

Hoshin kanri: A strategic planning system developed in Japan and North America over the past thirty years. Also known as strategic policy deployment. Metaphorical meanings include “ship in a storm going in the right direction” and “shining needle or compass.”

Hoshin planning: See *Hoshin kanri*.

Jidoka: Automation with a human mind. Jidoka means developing processes with both high capability (few defects made) and containment (defects contained in the zone).

Jishuken: Voluntary study groups; e.g., association suppliers might join to share experiences and thus deepen their understanding of critical concepts.

Kaizen: A small incremental improvement. Kaizen activity should involve everyone regardless of position.

Kanban: A small sign or signboard, an instruction to produce or supply something; usually a card; usually includes supplier and customer names, and information on transportation and storage; a central element of the just-in-time system. There are two types: production and withdrawal kanbans.

Management by objectives (MBO): The precursor to hoshin planning; introduced by Peter Drucker in his 1954 book, *The Practice of Management*.

Mental model: One’s assumptions about how the world works, based on experience, temperament, and upbringing; the invisible glasses that filter our experience and determine what we see.

Muda: Waste.

Mura: Unevenness.

Muri: Strain, either physical or mental; overburden.

Nemawashi: Literally means “to prepare a tree for transplanting;” refers to the formal and informal method of gaining consensus prior to the implementation of a hoshin or plan.

The new seven: Problem-solving tools developed in Japan and North America in the 1970s. They include the affinity diagram, fault tree, Process Decision Program Charts (PDPC), matrix, tree diagram, interrelationship digraph, and Gantt chart.

Pareto chart: A problem solving tool comprising a bar chart showing possible contributing factors in descending order; one of the Seven Quality Tools.

PDCA: The plan, do, check, act cycle developed by Walter Shewhart in the 1930s and refined by W. Edwards Deming.

Poka-yoke: An inexpensive robust device that eliminates the possibility of a defect by alerting the operator that an error has occurred.

Pull: To produce an item only when the customer asks for it. Typically, the customer “withdraws” the item and we “plug the gap” created thereby.

Push: To produce an item irrespective of actual demand; creates the muda of overproduction.

SMART: Simple, measurable, achievable, reasonable, and trackable. Refers to goals and targets.

Sensei: Teacher, one who has gone before.

The Seven Quality Tools: Problem solving tools developed in Japan and North America over the past century. They include the run chart, Pareto chart, histogram, control chart, checksheet, and scatter diagram.

Standard: The best way we know at this moment; standards in the lean system change as we discover better ways of working; a clear, simple image of what should be happening.

Store: A controlled inventory of items that is used to schedule production at an upstream process. Usually located near the upstream process to make customer requirements visible. Also called a supermarket.

Strategy Deployment: see *Hoshin Kanri*.

Supermarket: See *Store*.

Takt: The pace of production synchronized with the rate of sales.

Tree diagram: A tool used for mapping tasks for implementation; one of the new Seven Quality Tools; used in hoshin planning.

Total productive maintenance (TPM): An integrated set of activities aimed at maximizing equipment effectiveness by involving everyone in all departments at all levels, typically through small-group activities. TPM usually

entails implementing the 5S system, measuring the six big losses, prioritizing problems, and applying problem solving with the goal of achieving zero breakdowns.

Value Stream: The series of steps required to bring a product or service to the customer.

Value Stream Map: A diagram, usually hand drawn that shows the series of steps required to bring a product of service to a customer; also known as material and information flow diagram.

Work-in-process (WIP): Items between machines waiting to be processed.

Yokoten: Information sharing across the plant; sharing of common issues and countermeasures.

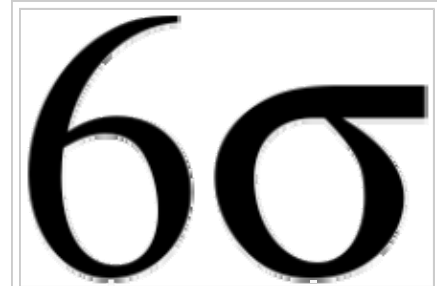
Six Sigma

From Wikipedia, the free encyclopedia
(Redirected from Six sigma)

Six Sigma is a business management strategy originally developed by Motorola, USA in 1986.^{[1][2]} As of 2010, it is widely used in many sectors of industry, although its use is not without controversy.

Six Sigma seeks to improve the quality of process outputs by identifying and removing the causes of defects (errors) and minimizing variability in manufacturing and business processes.^[3] It uses a set of quality management methods, including statistical methods, and creates a special infrastructure of people within the organization ("Black Belts", "Green Belts", etc.) who are experts in these methods.^[3] Each Six Sigma project carried out within an organization follows a defined sequence of steps and has quantified financial targets (cost reduction or profit increase).^[3]

The term *six sigma* originated from terminology associated with manufacturing, specifically terms associated with statistical modelling of manufacturing processes. The maturity of a manufacturing process can be described by a *sigma* rating indicating its yield, or the percentage of defect-free products it creates. A six-sigma process is one in which 99.99966% of the products manufactured are statistically expected to be free of defects (3.4 defects per million). Motorola set a goal of "six sigmas" for all of its manufacturing operations, and this goal became a byword for the management and engineering practices used to achieve it.



The often-used six sigma symbol.

Part of a series of articles on Industry



Manufacturing methods

Batch production • Job production

Continuous production

Improvement methods

LM • TPM • QRM • VDM

TOC • Six Sigma • RCM

Information & communication

ISA-88 • ISA-95 • ERP

SAP • IEC 62264 • B2MML

Process control

PLC • DCS

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- 2 Methods
 - 2.1 DMAIC
 - 2.2 DMADV or DFSS
 - 2.3 Quality management tools and methods used in Six Sigma
- 3 Implementation roles
 - 3.1 Certification
- 4 Origin and meaning of the term "six sigma process"
 - 4.1 Role of the 1.5 sigma shift
 - 4.2 Sigma levels

- 5 Software used for Six Sigma
- 6 Application
- 7 Criticism
 - 7.1 Lack of originality
 - 7.2 Role of consultants
 - 7.3 Potential negative effects
 - 7.4 Based on arbitrary standards
 - 7.5 Criticism of the 1.5 sigma shift
- 8 See also
- 9 References
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Historical overview

Six Sigma originated as a set of practices designed to improve manufacturing processes and eliminate defects, but its application was subsequently extended to other types of business processes as well.^[4] In Six Sigma, a defect is defined as any process output that does not meet customer specifications, or that could lead to creating an output that does not meet customer specifications.^[3]

Bill Smith first formulated the particulars of the methodology at Motorola in 1986.^[1] Six Sigma was heavily inspired by six preceding decades of quality improvement methodologies such as quality control, TQM, and Zero Defects,^{[5][6]} based on the work of pioneers such as Shewhart, Deming, Juran, Ishikawa, Taguchi and others.

Like its predecessors, Six Sigma doctrine asserts that:

- Continuous efforts to achieve stable and predictable process results (i.e., reduce process variation) are of vital importance to business success.
- Manufacturing and business processes have characteristics that can be measured, analyzed, improved and controlled.
- Achieving sustained quality improvement requires commitment from the entire organization, particularly from top-level management.

Features that set Six Sigma apart from previous quality improvement initiatives include:

- A clear focus on achieving measurable and quantifiable financial returns from any Six Sigma project.^[3]
- An increased emphasis on strong and passionate management leadership and support.^[3]
- A special infrastructure of "Champions," "Master Black Belts," "Black Belts," "Green Belts", etc. to lead and implement the Six Sigma approach.^[3]
- A clear commitment to making decisions on the basis of verifiable data, rather than assumptions and guesswork.^[3]

The term "Six Sigma" comes from a field of statistics known as process capability studies. Originally, it referred to the ability of manufacturing processes to produce a very high proportion of output within specification. Processes that operate with "six sigma quality" over the short term are assumed to produce long-term defect levels below 3.4 defects per million opportunities (DPMO).^{[7][8]} Six Sigma's implicit goal is to improve all processes to that level of quality or better.

Six Sigma is a registered service mark and trademark of Motorola Inc.^[9] As of 2006 Motorola reported over US\$17 billion in savings^[10] from Six Sigma.

Other early adopters of Six Sigma who achieved well-publicized success include Honeywell (previously known as AlliedSignal) and General Electric, where Jack Welch introduced the method.^[11] By the late 1990s, about two-thirds of the Fortune 500 organizations had begun Six Sigma initiatives with the aim of reducing costs and improving quality.^[12]

In recent years, some practitioners have combined Six Sigma ideas with lean manufacturing to yield a methodology named Lean Six Sigma.

Methods

Six Sigma projects follow two project methodologies inspired by Deming's Plan-Do-Check-Act Cycle. These methodologies, composed of five phases each, bear the acronyms DMAIC and DMADV.^[12]

- DMAIC is used for projects aimed at improving an existing business process.^[12] DMAIC is pronounced as "duh-may-ick".
- DMADV is used for projects aimed at creating new product or process designs.^[12] DMADV is pronounced as "duh-mad-vee".

DMAIC

The DMAIC project methodology has five phases:

- *Define* the problem, the voice of the customer, specifically.
- *Measure* key aspects of the current process and collect relevant data.
- *Analyze* the data to investigate and verify cause-and-effect relationships. Determine what the relationships are, and attempt to ensure that all factors have been considered. Seek out root cause of the defect under investigation.
- *Improve* or optimize the current process based upon data analysis using techniques such as design of experiments, poka yoke or mistake proofing, and standard work to create a new, future state process

DMADV or DFSS

The DMADV project methodology, also known as DFSS ("**D**esign **F**or **S**ix **S**igma"),^[12] features five phases:

- *Define* design goals that are consistent with customer demands and the enterprise strategy.
- *Measure* and identify CTQs (characteristics that are **C**ritical **T**o **Q**uality), product capabilities, production process capability, and risks.
- *Analyze* to develop and design alternatives, create a high-level design and evaluate design capability to select the best design.
- *Design* details, optimize the design, and plan for design verification. This phase may require simulations.
- *Verify* the design, set up pilot runs, implement the production process and hand it over to the

process owner(s).

Quality management tools and methods used in Six Sigma

Within the individual phases of a DMAIC or DMADV project, Six Sigma utilizes many established quality-management tools that are also used outside of Six Sigma. The following table shows an overview of the main methods used.

- | | |
|--|---|
| ■ 5 Whys | ■ Histograms |
| ■ Analysis of variance | ■ Quality Function Deployment (QFD) |
| ■ ANOVA Gauge R&R | ■ Pareto chart |
| ■ Axiomatic design | ■ Pick chart |
| ■ Business Process Mapping | ■ Process capability |
| ■ Cause & effects diagram (also known as fishbone or Ishikawa diagram) | ■ Quantitative marketing research through use of Enterprise Feedback Management (EFM) systems |
| ■ Chi-square test of independence and fits | ■ Regression analysis |
| ■ Control chart | ■ Root cause analysis |
| ■ Correlation | ■ Run charts |
| ■ Cost-benefit analysis | ■ SIPOC analysis (Suppliers, Inputs, Process, Outputs, Customers) |
| ■ CTQ tree | ■ Taguchi methods |
| ■ Design of experiments | ■ Taguchi Loss Function |
| ■ Failure mode and effects analysis (FMEA) | ■ TRIZ |
| ■ General linear model | |

Implementation roles

One key innovation of Six Sigma involves the "professionalizing" of quality management functions. Prior to Six Sigma, quality management in practice was largely relegated to the production floor and to statisticians in a separate quality department. Formal Six Sigma programs borrow martial arts ranking terminology to define a hierarchy (and career path) that cuts across all business functions.

Six Sigma identifies several key roles for its successful implementation.^[13]

- *Executive Leadership* includes the CEO and other members of top management. They are responsible for setting up a vision for Six Sigma implementation. They also empower the other role holders with the freedom and resources to explore new ideas for breakthrough improvements.
- *Champions* take responsibility for Six Sigma implementation across the organization in an integrated manner. The Executive Leadership draws them from upper management. Champions also act as mentors to Black Belts.
- *Master Black Belts*, identified by champions, act as in-house coaches on Six Sigma. They devote 100% of their time to Six Sigma. They assist champions and guide Black Belts and Green Belts. Apart from statistical tasks, they spend their time on ensuring consistent application of Six Sigma across various functions and departments.
- *Black Belts* operate under Master Black Belts to apply Six Sigma methodology to specific projects. They devote 100% of their time to Six Sigma. They primarily focus on Six Sigma project execution, whereas Champions and Master Black Belts focus on identifying projects/functions for Six Sigma.
- *Green Belts* are the employees who take up Six Sigma implementation along with their other job responsibilities, operating under the guidance of Black Belts.

Some organizations use additional belt colours, such as *Yellow Belts*, for employees that have basic training in Six Sigma tools.

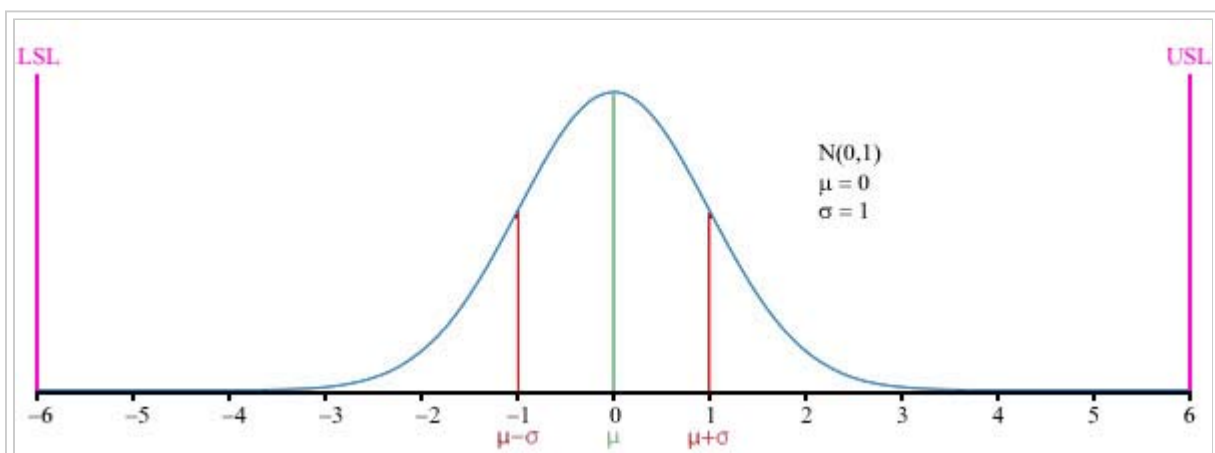
Certification

In the United States, Six Sigma certification for both Green and Black Belts is offered by the Institute of Industrial Engineers^[14] and by the American Society for Quality.^[15]

In addition to these examples, there are many other organizations and companies that offer certification. There currently is no central certification body, either in the United States or anywhere else in the world.

Origin and meaning of the term "six sigma process"

The term "six sigma



Graph of the normal distribution, which underlies the statistical assumptions of the Six Sigma model. The Greek letter σ (sigma) marks the distance on the horizontal axis between the mean, μ , and the curve's inflection point. The greater this distance, the greater is the spread of values encountered. For the curve shown above, $\mu = 0$ and $\sigma = 1$. The upper and lower specification limits (USL, LSL) are at a distance of 6σ from the mean. Because of the properties of the normal distribution, values lying that far away from the mean are extremely unlikely. Even if the mean were to move right or left by 1.5σ at some point in the future (1.5 sigma shift), there is still a good safety cushion. This is why Six Sigma aims to have processes where the mean is at least 6σ away from the nearest specification limit.

process" comes from the notion that if one has six standard deviations between the process mean and the nearest specification limit, as shown in the graph, practically no items will fail to meet specifications.^[8] This is based on the calculation method employed in process capability studies.

Capability studies measure the number of standard deviations between the process mean and the nearest specification limit in sigma units. As process standard deviation goes up, or the mean of the process moves away from the center of the tolerance, fewer standard deviations will fit between the mean and the nearest specification limit, decreasing the sigma number and increasing the likelihood of items outside specification.^[8]

Role of the 1.5 sigma shift

Experience has shown that processes usually do not perform as well in the long term as they do in the short term.^[8] As a result, the number of sigmas that will fit between the process mean and the nearest specification limit may well drop over time, compared to an initial short-term study.^[8] To account for this real-life increase in process variation over time, an empirically-based 1.5 sigma shift is introduced into the calculation.^{[8][16]} According to this idea, a process that fits six sigmas between the process mean and the nearest specification limit in a short-term study will in the long term only fit 4.5 sigmas – either because the process mean will move over time, or because the long-term standard deviation of the process will be greater than that observed in the short term, or both.^[8]

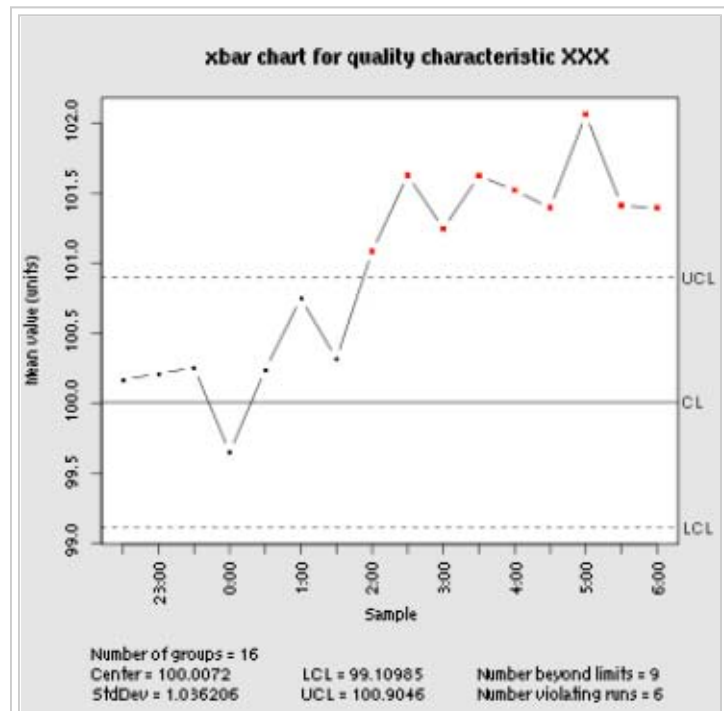
Hence the widely accepted definition of a six sigma process as one that produces 3.4 defective parts per million opportunities (DPMO). This is based on the fact that a process that is normally distributed will have 3.4 parts per million beyond a point that is 4.5 standard deviations above or below the mean (one-sided capability study).^[8] So the 3.4 DPMO of a "Six Sigma" process in fact corresponds to 4.5 sigmas, namely 6 sigmas minus the 1.5 sigma shift introduced to account for long-term variation.^[8] This takes account of special causes that may cause a deterioration in process performance over time and is designed to prevent underestimation of the defect levels likely to be encountered in real-life operation.^[8]

Sigma levels

See also: Three sigma rule

The table^{[17][18]} below gives long-term DPMO values corresponding to various short-term sigma levels.

Note that these figures assume that the process mean will shift by 1.5 sigma toward the side with the critical specification limit. In other words, they assume that after the initial study determining the short-term sigma level, the long-term C_{pk} value will turn out to be 0.5 less than the short-term C_{pk} value. So, for example, the DPMO figure given for 1 sigma assumes that the long-term process mean will be 0.5 sigma *beyond* the specification limit ($C_{pk} = -0.17$), rather than 1 sigma *within* it, as it was in the short-term study ($C_{pk} = 0.33$). Note that the defect percentages only indicate defects exceeding the specification limit to which the process mean is nearest. Defects beyond the far specification limit are not included in the percentages.



A control chart depicting a process that experienced a 1.5 sigma drift in the process mean toward the upper specification limit starting at midnight. Control charts are used to maintain 6 sigma quality by signaling when quality professionals should investigate a process to find and eliminate special-cause variation.

				C_{pk}	C_{pk}
1	691,462	69%	31%	0.33	−0.17
2	308,538	31%	69%	0.67	0.17
3	66,807	6.7%	93.3%	1.00	0.5
4	6,210	0.62%	99.38%	1.33	0.83
5	233	0.023%	99.977%	1.67	1.17
6	3.4	0.00034%	99.99966%	2.00	1.5
7	0.019	0.0000019%	99.9999981%	2.33	1.83

Software used for Six Sigma

Main article: List of Six Sigma software packages

Application

Main article: List of Six Sigma companies

Six Sigma mostly finds application in large organizations.^[19] An important factor in the spread of Six Sigma was GE's 1998 announcement of \$350 million in savings thanks to Six Sigma, a figure that later grew to more than \$1 billion.^[19] According to industry consultants like Thomas Pyzdek and John Kullmann, companies with less than 500 employees are less suited to Six Sigma implementation, or need to adapt the standard approach to make it work for them.^[19] This is due both to the infrastructure of Black Belts that Six Sigma requires, and to the fact that large organizations present more opportunities for the kinds of improvements Six Sigma is suited to bringing about.^[19]

Criticism

Lack of originality

Noted quality expert Joseph M. Juran has described Six Sigma as "a basic version of quality improvement", stating that "there is nothing new there. It includes what we used to call facilitators. They've adopted more flamboyant terms, like belts with different colors. I think that concept has merit to set apart, to create specialists who can be very helpful. Again, that's not a new idea. The American Society for Quality long ago established certificates, such as for reliability engineers."^[20]

Role of consultants

The use of "Black Belts" as itinerant change agents has (controversially) fostered an industry of training and certification. Critics argue there is overselling of Six Sigma by too great a number of consulting firms, many of which claim expertise in Six Sigma when they only have a rudimentary understanding of the tools and techniques involved.^[3]

Potential negative effects

A *Fortune* article stated that "of 58 large companies that have announced Six Sigma programs, 91 percent have trailed the S&P 500 since". The statement is attributed to "an analysis by Charles Holland of consulting firm Qualpro (which espouses a competing quality-improvement process)."^[21] The summary of the article is that Six Sigma is effective at what it is intended to do, but that it is "narrowly designed to fix an existing process" and does not help in "coming up with new products or disruptive technologies." Advocates of Six Sigma have argued that many of these claims are in error or ill-informed.^{[22][23]}

A *BusinessWeek* article says that James McNerney's introduction of Six Sigma at 3M may have had the effect of stifling creativity. It cites two Wharton School professors who say that Six Sigma leads to incremental innovation at the expense of blue-sky work.^[24] This phenomenon is further explored in the book, *Going Lean*, which describes a related approach known as lean dynamics and provides data to show that Ford's "6 Sigma" program did little to change its fortunes.^[25]

Based on arbitrary standards

While 3.4 defects per million opportunities might work well for certain products/processes, it might not operate optimally or cost effectively for others. A pacemaker process might need higher standards, for example, whereas a direct mail advertising campaign might need lower standards. The basis and justification for choosing 6 (as opposed to 5 or 7, for example) as the number of standard deviations is not clearly explained. In addition, the Six Sigma model assumes that the process data always conform to the normal distribution. The calculation of defect rates for situations where the normal distribution model does not apply is not properly addressed in the current Six Sigma literature.^[3]

Criticism of the 1.5 sigma shift

The statistician Donald J. Wheeler has dismissed the 1.5 sigma shift as "goofy" because of its arbitrary nature.^[26] Its universal applicability is seen as doubtful.^[3]

The 1.5 sigma shift has also become contentious because it results in stated "sigma levels" that reflect short-term rather than long-term performance: a process that has long-term defect levels corresponding to 4.5 sigma performance is, by Six Sigma convention, described as a "6 sigma process."^{[8][27]} The accepted Six Sigma scoring system thus cannot be equated to actual normal distribution probabilities for the stated number of standard deviations, and this has been a key bone of contention about how Six Sigma measures are defined.^[27] The fact that it is rarely explained that a "6 sigma" process will have long-term defect rates corresponding to 4.5 sigma performance rather than actual 6 sigma performance has led several commentators to express the opinion that Six Sigma is a confidence trick.^[8]

See also

- Business process
- Design for Six Sigma
- Total quality management
- Total productive maintenance

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NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED

TO: David G. Strunce, President and CEO

FIRM NAME

Scientific Protein Laboratories LLC

STREET ADDRESS

700 E. Main Street

CITY, STATE AND ZIP CODE

Waunakee, WI 53597

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DURING AN INSPECTION OF YOUR FIRM (I) (WE) OBSERVED:

OBSERVATION #1

Equipment used in the manufacture of API intermediates is not of appropriate design and has not been qualified to ensure it does not alter the quality of the intermediate or API.

Specifically, wet cake pancreatin (b) (4) is stored in (b) (4) drums for up to (b) (4) weeks prior to drying. When it is unloaded into the dryer a stainless steel shovel and stainless steel pitch fork is used to transfer material out of the drum. On 8/3/10 transfer of wet cake from lot #1208-1779 was observed using these utensils. Half way through the transfer, an approximately quarter inch piece of blue plastic shaving was observed in the wet cake and an approximately half inch piece of blue plastic was hanging from a gouge on the inside of the drum. The firm determined that the sharp edges of the utensils were scraping the sides of the drum and resulting in plastic shavings. An inspection of drums that had been used in production of previous lots, which had been cleaned and were ready for further use, were found to have scrapes, gouges, hanging pieces of plastic, and missing pieces out of their inner surfaces.

Additionally, (b) (4) drums are used to store wet cake pancreatin (b) (4) for up to (b) (4) weeks. These new (b) (4) drums replaced (b) (4) drums in production on 7/7/10. No extractable/leachable study has been completed on the (b) (4) drums to date.

Prior to 7/7/10, (b) (4) drums were used in production. These old drums were also observed to have scrapes, gouges, hanging pieces of plastic, and missing pieces out of their inner surfaces.

OBSERVATION #2

You did not adequately investigate a complaint that affected product quality and did not extend the investigation to other lots that may have been associated with the complaint.

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TYPE OF ESTABLISHMENT INSPECTED

API Manufacturer

Specifically, the SPL R&D department received a complaint that made them aware of potential Oversulfated Chondroitin Sulfate (OSCS) in Heparin finished product lot 1035-0778 on 10/9/08. The quality department did not initiate a formal investigation into this complaint until 9/9/09.

SPL concluded raw material lot #060600189 contained OSCS contamination. This raw material was used to manufacture finished Heparin API lots #1035-0778 and #1035-0780. Both lots were fully distributed. An investigation into the raw material lot and lot #1035-0778 was conducted, but not completed until 6/1/10. There was no formal investigation into lot #1035-0780.

OBSERVATION #3

You did not adequately evaluate and qualify your contract testing laboratory.

Specifically, SPL did not qualify (b) (4) per SOP 65-9663 "Qualification and Use of Contract Laboratories" prior to use. (b) (4) has been used for release testing and historical testing for (b) (4) of (b) (4) samples since 4/13/10.

OBSERVATION #4

You did not adequately evaluate your suppliers of raw ingredients.

Specifically, SOP 50-0044 "Porcine Mucosa/Hash Gut/Resin and Pancreas Gland Supplier Audits" states: "Each slaughterhouse...will be audited once every two years." At the initiation of this inspection the following approved suppliers that had not been audited within the past two years:

(b) (4) Last audited 2/26/08
(b) (4) Last audited 6/18/08.
(b) (4) Last audited 6/19/08.
(b) (4) Last audited 2/28/08.

The following slaughterhouses have recently been audited, but had exceeded the two year time frame between

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE  	EMPLOYEE(S) NAME AND TITLE (Print or Type) Sandra A. Hughes, CSO Justin A. Boyd, CSO	DATE ISSUED 09/03/2010
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DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

Use this check box to generate
the required 483 statement on page
1 for medical device observations. ☐

DISTRICT OFFICE ADDRESS AND PHONE NUMBER

Minneapolis District
250 Marquette Avenue Suite 600
Minneapolis, MN 55401
612-334-4100

Industry Information: www.fda.gov/oc/industry

DATE(S) OF INSPECTION

7/28-30/10, 8/2-3, 5-6, 11, 13/10, 9/2-3/10

FEI NUMBER

2111173

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED

TO: David G. Strunce, President and CEO

FIRM NAME

Scientific Protein Laboratories LLC

STREET ADDRESS

700 E. Main Street

CITY, STATE AND ZIP CODE

Waukegan, WI 53597

TYPE OF ESTABLISHMENT INSPECTED

API Manufacturer

previous audits:

- (b) (4) Last audited 7/13/10 and prior to that on 3/28/08.

- (b) (4) Last audited 7/09/10 and prior to that on 5/14/08.

Further, shipments of glands that originated from (b) (4) were received 1/29/10, 6/9/10, and 6/22/10. The annual re-qualification for this supplier was not completed per SOP 76-0003 "Alternate/New Raw Material Vendor Approval and Annual Qualification".

SEE
REVERSE
OF THIS
PAGE

EMPLOYEE(S) SIGNATURE

Sandra A. Hughes
Justin A. Boyd

EMPLOYEE(S) NAME AND TITLE (Print or Type)

Sandra A. Hughes, CSO
Justin A. Boyd, CSO

DATE ISSUED

09/03/2010