Mount Wachusett Community College

QUALITY SYSTEMS in BIOSCIENCE MANUFACTURING

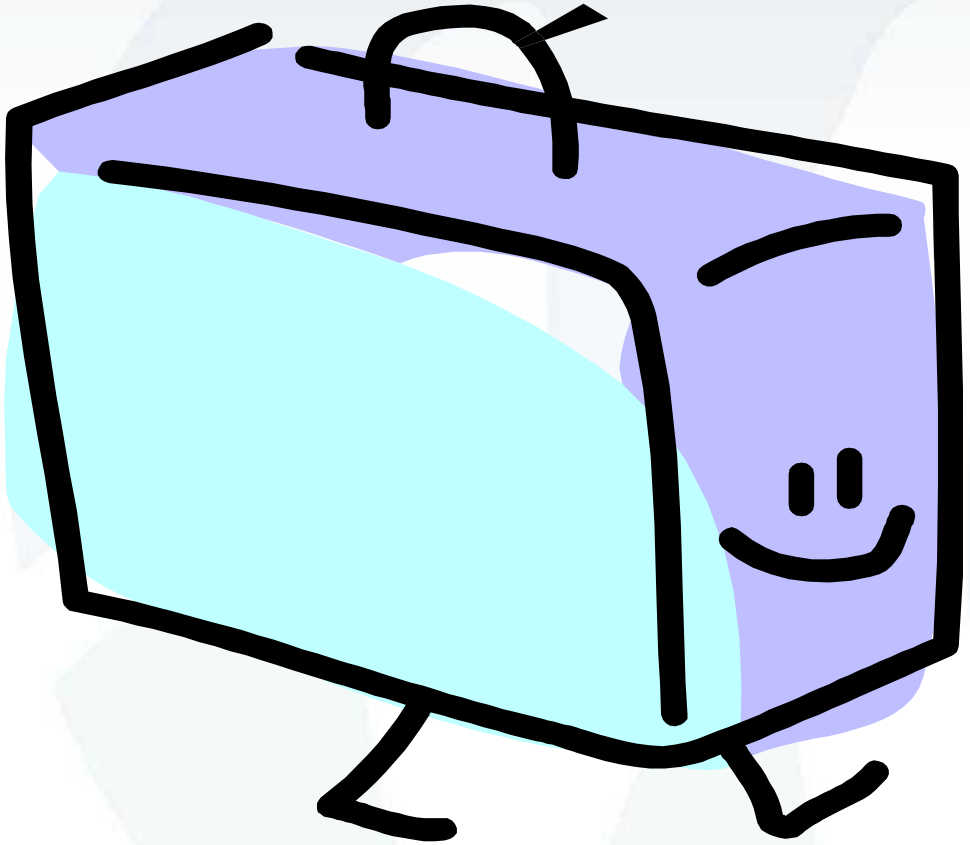
BIOMAN Conference July 2015

Prepared by Gretchen Ingvason as part of NSF ATE Grant #1304474 -(National Science Foundation Advanced Technical Education)

AGENDA

- Concepts in Quality
- Quality Systems
- Quality Operations
- Investigations
- Bring it to the Classroom

MY BACKGROUND



BIOTECHNOLOGY

.. feeding, fueling and healing the world.

CONCEPTS IN QUALITY

What is Quality?
Industry Overview
Standards & Regulations

QUALITY IN MANUFACTURING

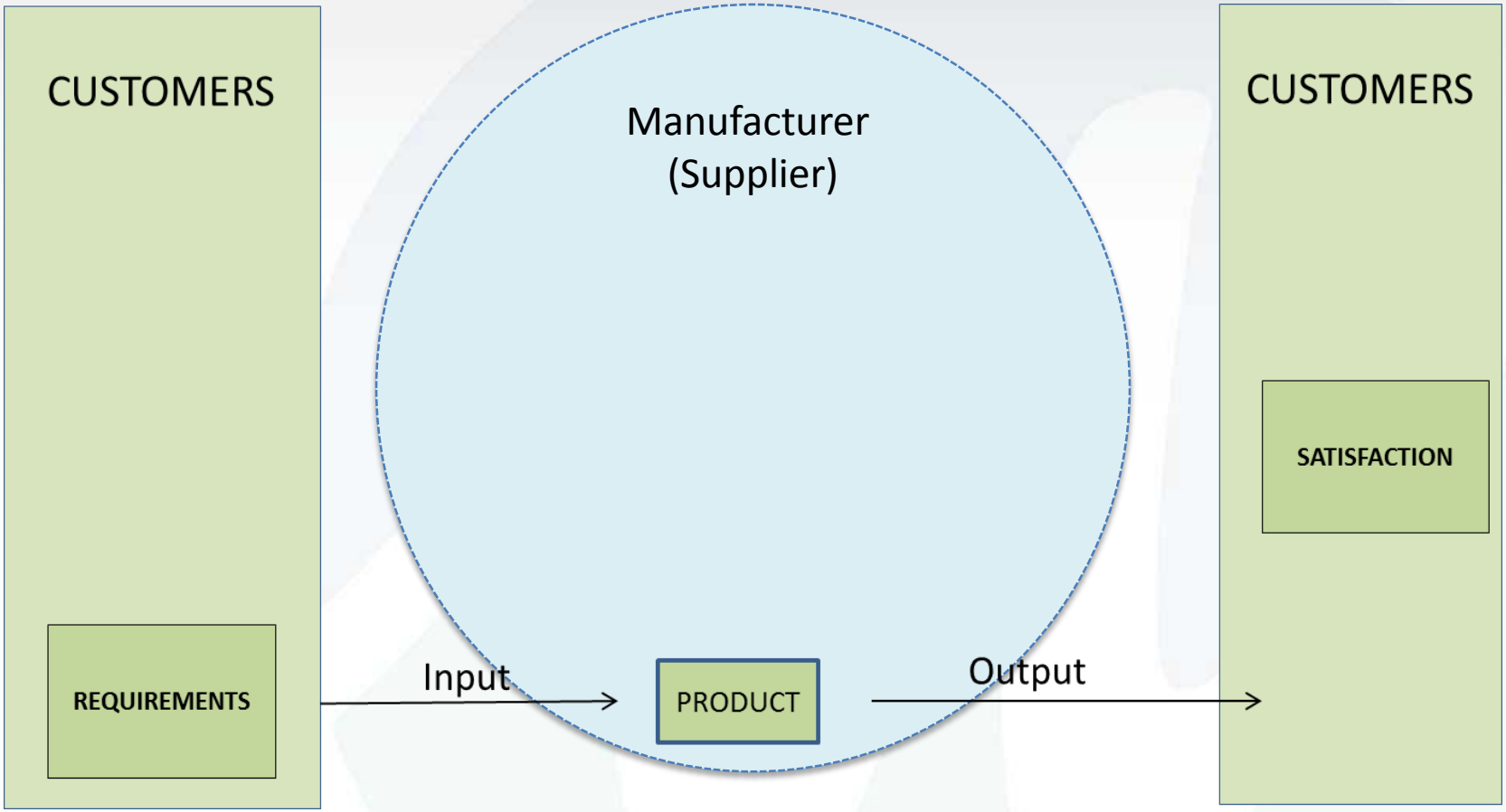
- Quality is an important component of cost of goods sold.
- Tracked through multiple measures.
- Lack of quality can lead to product and company failure.

WHAT IS QUALITY

Quality is a product (or service) with the *features and characteristics* which determine *desirability* and can be *controlled* to *meet certain basic requirements.*

- Who determines desirability of features and/or characteristics?
- Why are they desirable?
- What are the requirements that can be controlled?
- How is it known if the requirements are met?

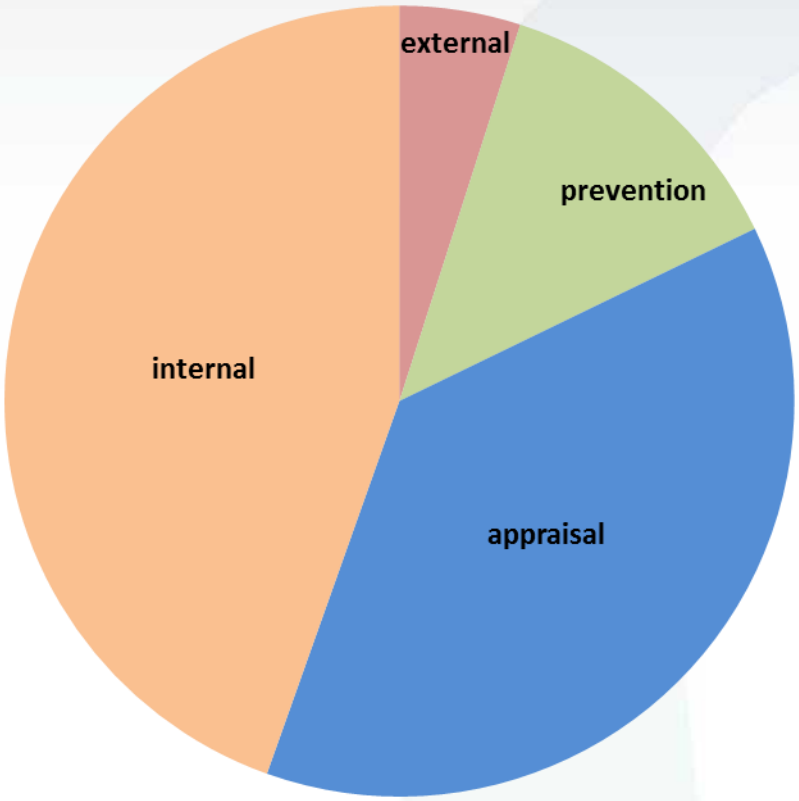
Quality is determined by the Customer (end-user) based on their expectation and needs.


CUSTOMERS
Manufacturer
(Supplier)
CUSTOMERS
SATISFACTION
REQUIREMENTS
Input
PRODUCT
Output

QUALITY ORGANIZATIONS

- ***Regulatory:*** Government organizations with legal oversight of industry
  - US FDA, European Union, etc.
- ***Independent:*** Organizations providing external review of industry processes
  - International Organization for Standardization (ISO)
  - ANSI (American National Standards Institute)
  - USP (US Pharmacopeia Convention)
- ***Trade:*** Organizations supported by industry representing common interests and processes
  - American Society for Quality (ASQ)
  - ASTM International (American Society for Testing & Materials)

COST OF QUALITY



- Internal
  - Scrap, Rework
- Appraisal
  - Material Receipt Measurement
  - In-process/Final Inspection
- Prevention
  - Improvement, Planning
- External
  - Returns, Warranty

Quality is a value that **must be built into** the product.
Quality **cannot be inspected into** the product

Quality – Career Pathways

- Multitude of industries
  - Pharmaceutical, Biotechnology, Medical Device, Automotive, Aerospace, Plastics, Food and Beverage, etc.
- ASQ Certifications (www.asq.org)
  - Certified Quality Improvement Associate
  - Certified Process Analyst
  - Certified Quality Inspector
  - Certified Quality Technician
  - Certified Calibration Technician
- Career Path
  - Quality Engineering
  - Regulatory Specialist
  - Utilize (leverage) current experience
- Entry into Engineering Technology or 4-year degree

VARIOUS INDUSTRIES & SECTORS

- Manufacturing
  - Corporate offices, Plants
  - Controlled Environments
- Service
  - Corporate Offices
  - Field work

MANUFACTURING

- Aerospace
  - Complete vehicles, components
- BioTechnology
- Chemicals
  - Adhesives, paint, pesticides, soaps
- Computer & Electronics
  - Audio/video, components, etc.
- Fabricated Metal Products
  - heat treating, engraving, nails,
- Foods
  - Animal feed, seasonings, snacks
- Machinery
  - Mowers, HVAC, assembly equipment
- Medical Devices & Supplies
  - Pacemakers, gurneys, filters
- Measurement Systems
  - Gages, Vision Systems, CMM
- Paper Products
  - Boxes, gift wrap, diapers
- Pharmaceuticals
  - Prescription, over-the-counter
- Rubber & Plastic Products
  - Tires, hoses, bags, pipes
- Transportation & Parts
  - Cars, trucks, boats, components
- Various Retail Goods
  - Toys, clothing, sporting goods

SERVICE

- Construction
  - Buildings, Infrastructure, roofing
- Consulting
  - Management, Scientific, technical
- Educational
  - Training, K-12, Secondary
- Financial & Insurance
  - Banks, Mortgages, Brokers
- Government /Public Admin
  - Judicial, security, fire protection
- Healthcare
  - Blood banks, diagnostic labs
- Information Services
  - Publishing, archiving
- Inspection Services
  - Residential, Power plants, Electrical
- Retail
  - Department Stores, Auto Dealers
- Social Services
  - Relief Services, Vocational Rehab
- Scientific / Technical
  - Testing Services, Engineering Firms

BIOTECHNOLOGY - Careers

- Agriculture / Aquaculture
  - Protect animals/crops from disease
  - Growing plants/animals in water
- Biodefense
  - Protect air/food/water from pathogenic microorganisms
- Biofuels
  - Diesel/ethanol purified from natural sources
- Biopharmaceuticals
  - genomics, vaccines
- Cosmetics
  - Discover and manufacture components
- Environmental Monitoring
  - Lab methods (i.e. microarrays) used to monitor air/water/soil
- Food Safety
  - Identify pathogens or chemical additives and their source
  - Track source of meat (illegal/poached)
- Forensics
  - Criminal investigations (DNA)
- Medical Diagnostics
  - Various tests

QUALITY SYSTEMS

ISO and FDA

QUALITY SYSTEMS

- Quality is a product (or service) with the *features and characteristics* which determine *desirability* and can be *controlled* to *meet certain basic requirements.*

- Quality System
  - Say what you do (documents)
  - Do what you say (training)
  - Record what you did (write it down, quality records)
  - Check the results (analysis)
  - Act on the difference (improvement)

Quality is determined by the Customer (end-user) based on their expectation and needs.

QUALITY SYSTEMS

- International Organization of Standardization (ISO)
  - ISO 9001:2008 Quality Management Systems – Requirements
  - ISO 13485:2003 Medical Devices – Quality Management Systems – Requirements for Regulatory Purposes
  - ISO/IEC 17025:2005 General Requirements and Competencies of Testing and Calibration Laboratories
  - ISO/TS 16949 (Automotive)
  - AS 9001 (Aerospace)

QUALITY SYSTEMS

- US Food & Drug Administration (FDA)
  - 21CFR (Code of Federal Regulations)
    - Part 210/211 Pharmaceuticals
    - Part 600/601/610 Biologics
    - Part 820 Medical Device
  - International Counterparts
    - Japan – Pharmaceutical & Medical Device Agency
    - Europe – European Directives
    - Canada –Health Canada

CODE OF FEDERAL REGULATIONS (CFR)

- CFR is the codification of the general and permanent rules and regulations (sometimes called administrative law)
- The titles are broken down into:
  Chapters, Parts , Sections , and Paragraphs

Example: 21 CFR 820.30(d) (1)
would read Title 21, Part 820, Section 30, Paragraph (d)(1)

CODE OF FEDERAL REGULATIONS (CFR)

Title 1	General Provisions
Title 2	Grants and Agreements
Title 3	The President
Title 4	Accounts
Title 5	Administrative Personnel
Title 6	Domestic Security
Title 7	Agriculture
Title 8	Aliens and Nationality
Title 9	Animals and Animal Products
Title 10	Energy
Title 11	Federal Elections
Title 12	Banks and Banking
Title 13	Business Credit and Assistance
Title 14	Aeronautics & Space (aka Federal Aviation Regulations)
Title 15	Commerce and Foreign Trade
Title 16	Commercial Practices
Title 17	Commodity and Securities Exchanges
Title 18	Conversation of Power & Water Resources
Title 19	Customs Duties
Title 20	Employee's Benefits
Title 21	Food and Drugs
Title 22	Foreign Relations
Title 23	Highways
Title 24	Housing & Urban Development
Title 25	Indians
Title 26	Internal Revenue (aka Treasury Regulations)
Title 27	Alcohol, Tobacco & Firearms
Title 28	Judicial Administration
Title 29	Labor
Title 30	Mineral Resources
Title 31	Money and Finance: Treasury
Title 32	National Defense
Title 33	Navigation & Navigable Waters
Title 34	Education
Title 35	Reserved (Formerly Panama Canal)
Title 36	Parks, Forests, and Public Property
Title 37	Patents, Trademarks, and Copyrights
Title 38	Pensions, Bonuses & Veterans Relief
Title 39	Postal Service
Title 40	Protection of Environment
Title 41	Public Contacts and Property Management
Title 42	Public Health
Title 43	Public Lands: Interior
Title 44	Emergency Management & Assistance
Title 45	Public Welfare
Title 46	Shipping
Title 47	Telecommunication
Title 48	Federal Acquisition Regulations Systems
Title 49	Transportation
Title 50	Wildlife & Fisheries

cGXP

- cGXP -- Current Good [ ] Practices
  - Manufacturing *(cGMP)*
    - Pharmaceutical
    - Medical Device
  - Laboratory *(cGLP)*
  - Clinical *(cGCP)*

cGXP

- cGXP -- Current Good [ ] Practices
  - Manufacturing *(cGMP)*
    - Pharmaceutical
    - Medical Device

"… practices required in order to conform to guidelines recommended by agencies that control authorization and licensing for manufacture and sale of … drug products, and active pharmaceutical products. These guidelines provide minimum requirements that a … manufacturer must meet to assure that the products are of high quality and do not pose any risk to the consumer or public …" (Wikapedia.com)

  - Laboratory *(cGLP)*
  - Clinical *(cGCP)*

cGXP

- cGXP -- Current Good [ ] Practices
  - Manufacturing *(cGMP)*
    - Pharmaceutical
    - Medical Device
  - Laboratory *(cGLP) (non-clinical)*

"..embodies a set of principles that provides a framework within which laboratory studies are planned, performed, monitored, recorded, reported and archived. These studies are undertaken to generate data by which the hazards and risks to users, consumers and third parties, including the environment, can be assessed … GLP helps assure regulatory authorities that the data submitted are a true reflection of the results obtained during the study and can therefore be relied upon when making risk/safety assessments. " *(Wikapedia.com)*

  - Clinical *(cGCP)*

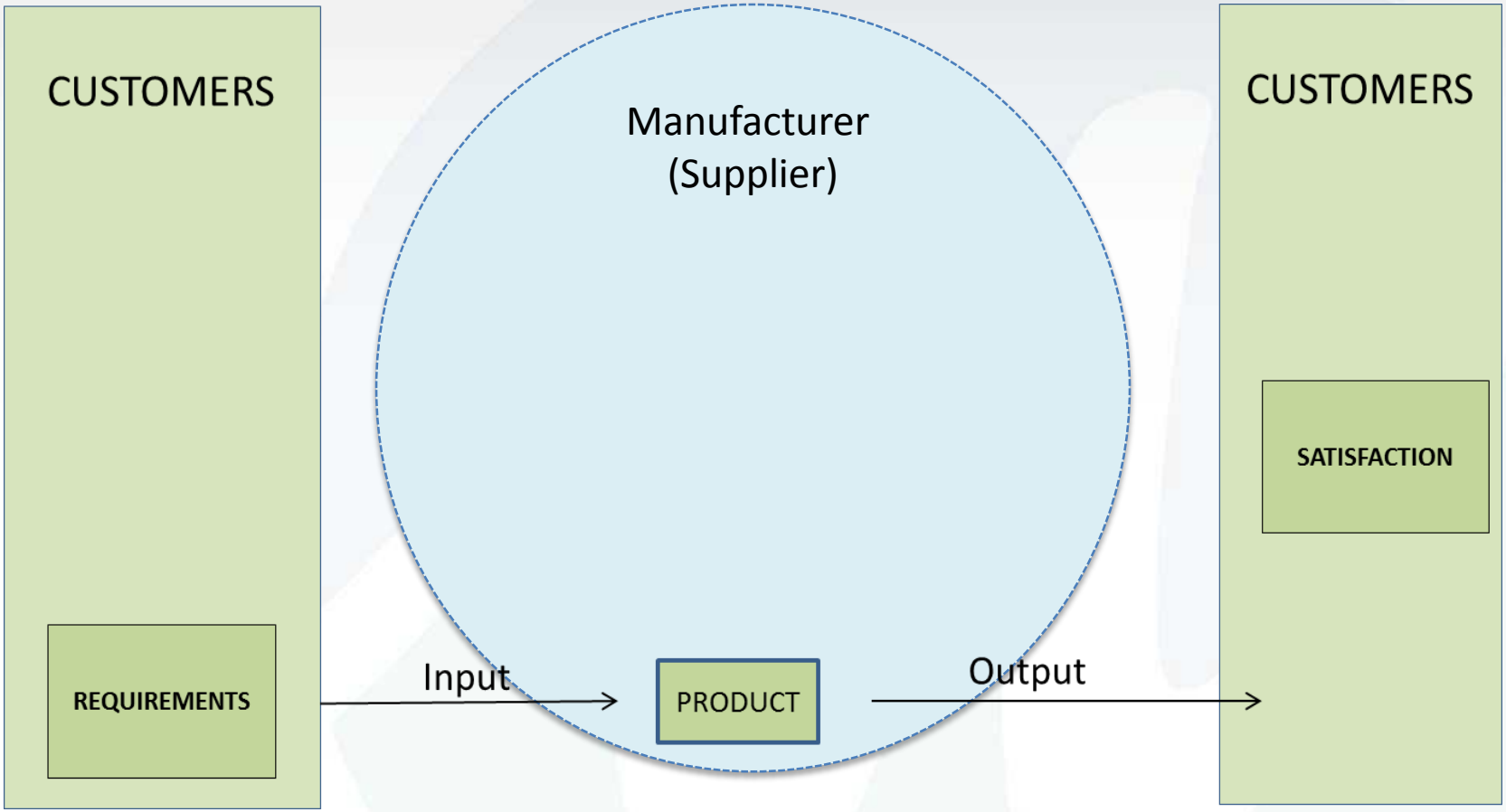
cGXP

- cGXP -- Current Good [ ] Practices
  - Manufacturing *(cGMP)*
    - Pharmaceutical
    - Medical Device
  - Laboratory *(cGLP) (non-clinical)*
  - Clinical *(cGCP)*

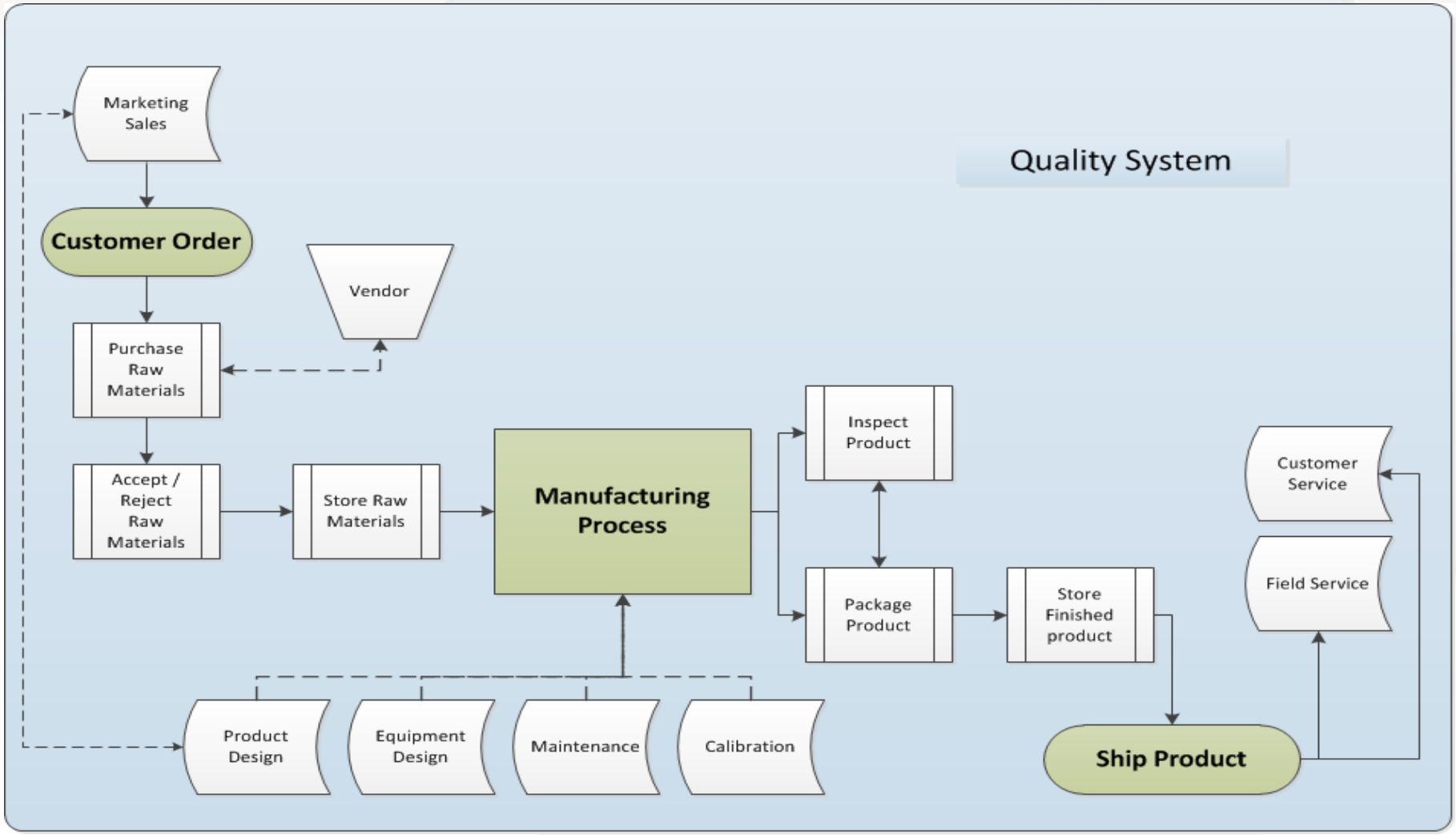
*"… enforces tight guidelines on **ethical aspects of a clinical study.** High standards are required in terms of comprehensive documentation for the clinical protocol, record keeping, training, and facilities, including computers and software… GCP guidelines include protection of human rights for the subjects and volunteers in a clinical trial. It also provides **assurance of the safety and efficacy of the newly developed compounds**…" (Wikapedia.com)*

QUALITY OPERATIONS

Incoming Inspection
Product Release
Manufacturing Support


CUSTOMERS
Manufacturer
(Supplier)
CUSTOMERS
SATISFACTION
REQUIREMENTS
Input
PRODUCT
Output

PROCESS FLOW - MANUFACTURING

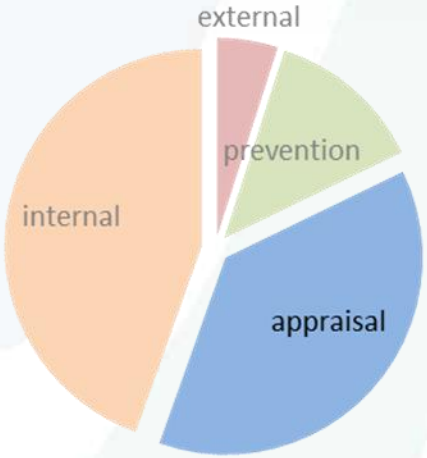


QUALITY SYSTEMS

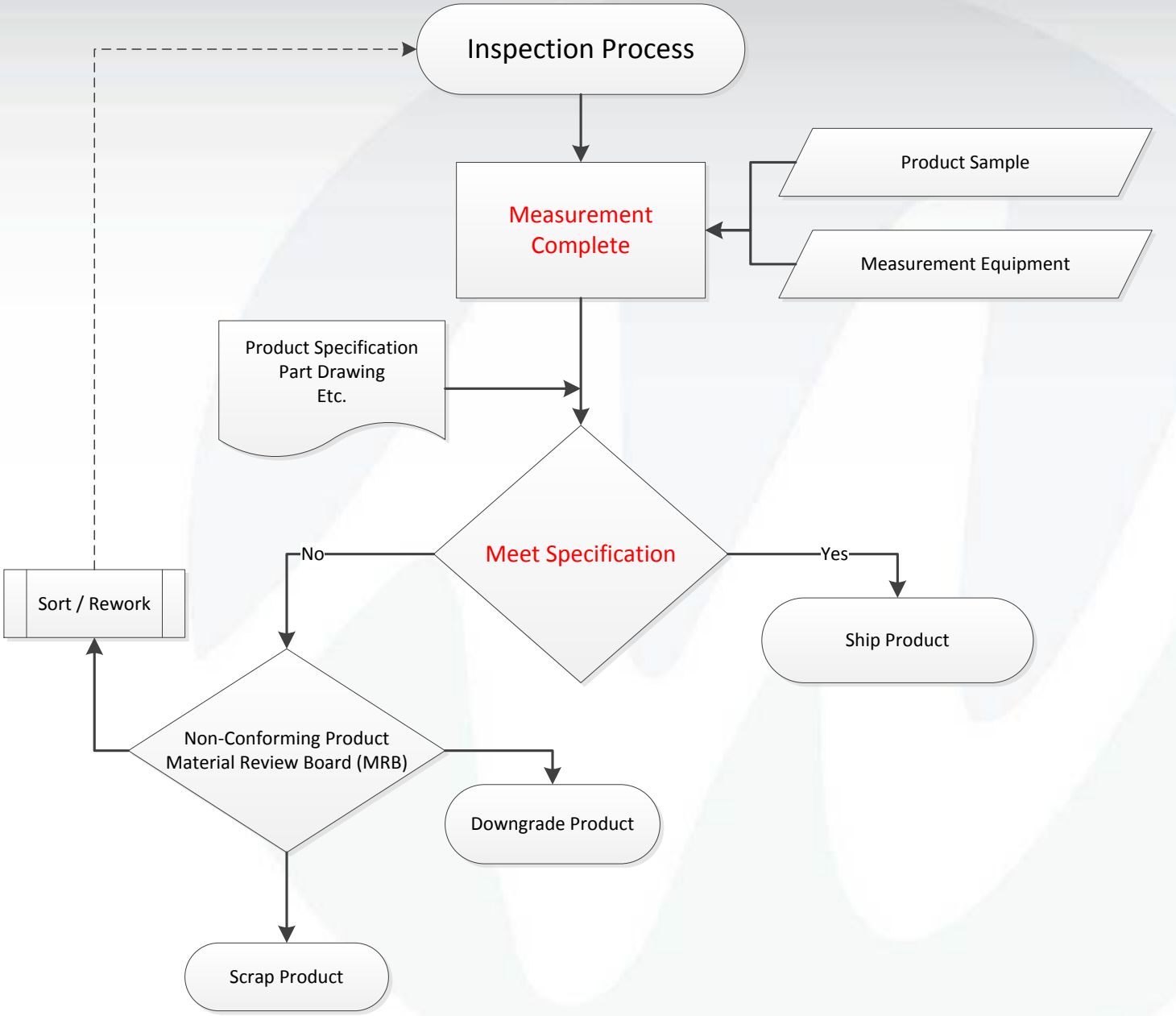
- Say what you do (documents)
- Do what you say (training)
- Record what you did (write it down, quality records)
- Check the results (analysis)
- Act on the difference (improvement)

INSPECTION

- Customers want expectations and needs met consistently
  - Fitness for use
  - Form is free of defect
  - Functions as intended
- Evaluate product quality by comparing measurement results with specifications
- Inspection process:
  - Measurement of sample
  - Comparison against specification
  - Decision based on results
  - Corrective action, if necessary



Inspection is after the fact –
materials used, product built, labor spent



Work supported by part of NSF ATE Grant #1304474

MEASUREMENT

- Measurement is a method for evaluating a property or characteristic of an object and describing it with a numerical or nominal value.
  - Dimensional (e.g. length, diameter, volume)
  - Functional (e.g. flow rate, tensile strength)
  - Chemical (e.g. material type, pH, etc.)
  - Service (e.g. time between calls, maintenance response, etc.)
  - Attribute (e.g. color, clarity, etc.)
  - etc.

ACCURACY vs PRECISION

Accurate but not precise

Precise but not accurate

Neither accurate nor precise

Accurate And Precise

METROLOGY PROGRAM

- Measurement Fundamentals
  - Methods, equipment
- Calibration System
  - Verification

METROLOGY PROGRAM

- **Measurement Fundamentals**
  - Methods
  - System
  - Capability
  - Equipment specifications
  - Environmental Controls
  - Standards Usage
  - Confidence (Uncertainty) Programs
  - Data

How to trust the results

METROLOGY PROGRAM

- **Calibration System**
  - Adequacy of equipment & standards
  - Procedures (Methods)
  - Internal Process / External Vendor program
  - Intervals
  - Quality (Confidence)
  - Scheduling
  - Environmental Controls
  - Software Validation
  - Labels
  - Measurement Traceability

How to trust the equipment/tools

INSPECTION TECHNIQUES

- Qualitative or Quantitative
- Destructive or Non-Destructive
- 100% or Sample

INSPECTION PROCESS – DATA ANALYSIS

- Statistical Analysis
  - Descriptive – organization, summarization & display of data
  - Inferential –uses sample to draw conclusions about a population
- Understanding data
  - Measures of central tendency (mean, median, mode)
  - Measures of dispersion (range, variance, standard deviation)
  - Measures of shape (normal distribution, weibull, etc.)

SEVEN QUALITY TOOLS

1. Flow Chart / Run Chart
2. Check Sheet
3. Histogram
4. Scatter Plot (Diagram)
5. Control Charts
6. Pareto Chart
7. Cause and Effect Diagram (a.k.a. Ishikawa or Fishbone)

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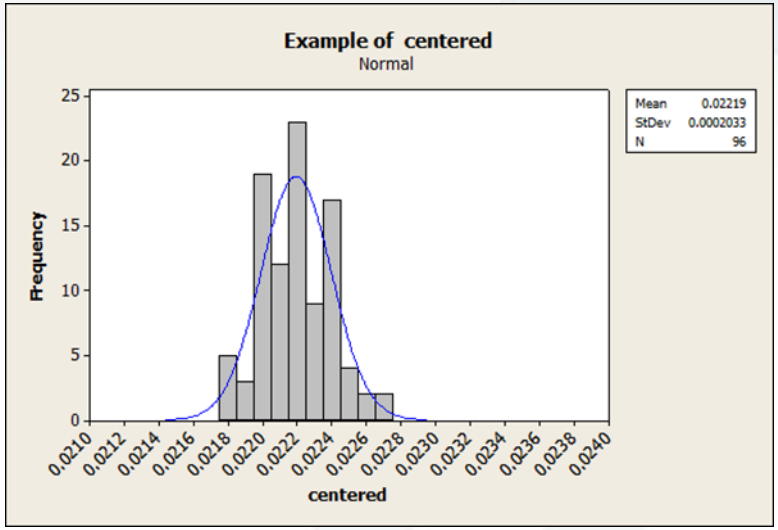
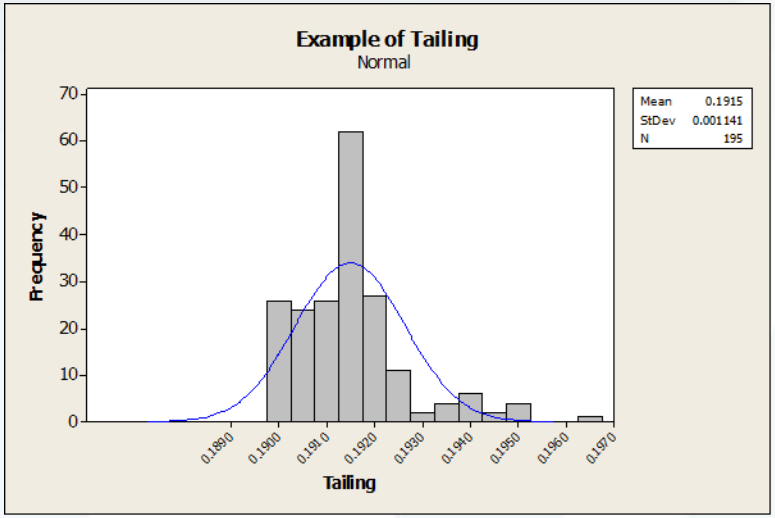
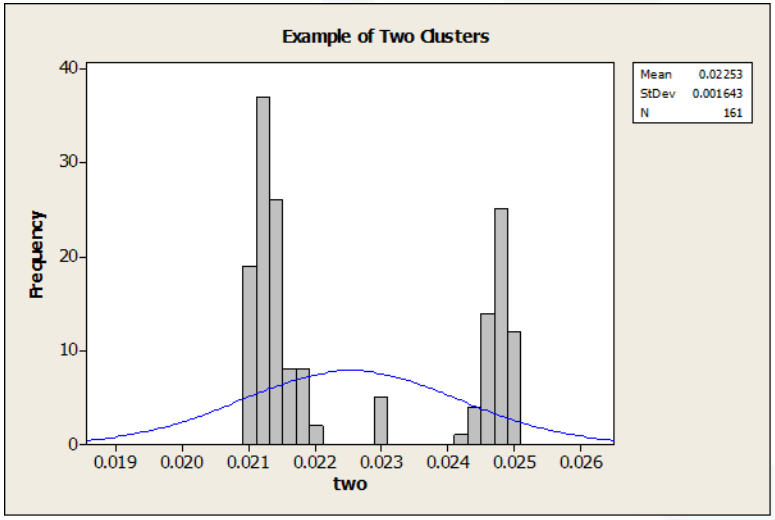
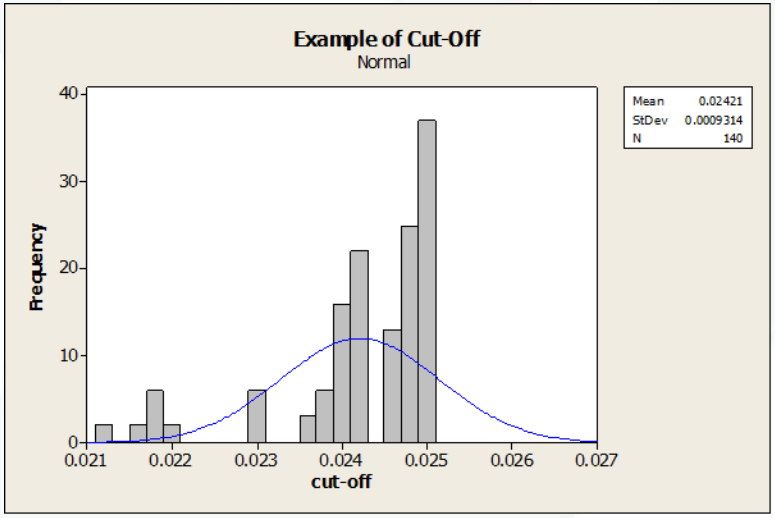
HISTOGRAM EXAMPLE

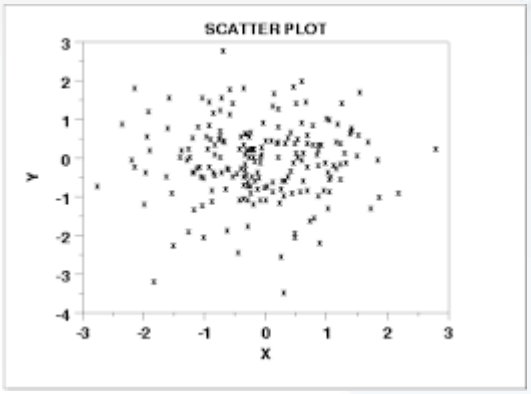








SCATTER PLOT (DIAGRAM)



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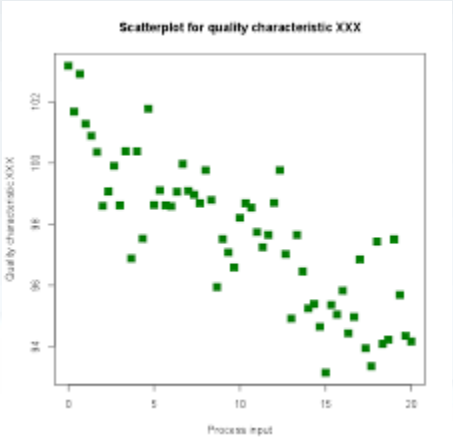
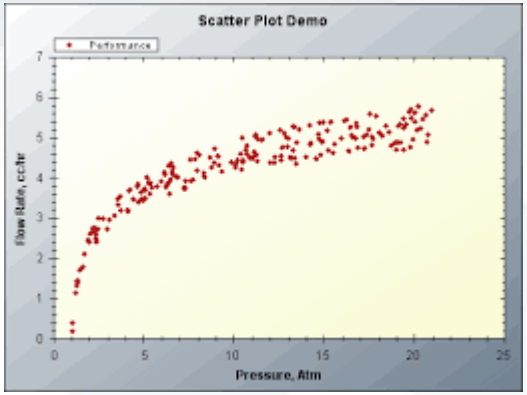
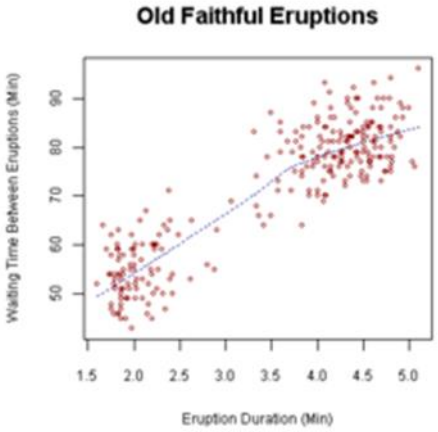


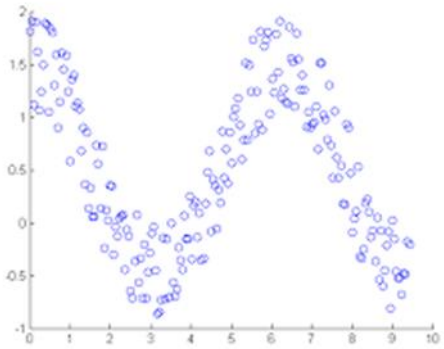
Negative linear



Positive non-linear



Clusters



Cyclic

SEVEN QUALITY TOOLS

1. Flow Chart / Run Chart
2. Check Sheet
3. Histogram
4. Scatter Plot (Diagram)
5. Control Charts
6. Pareto Chart
7. Cause and Effect Diagram (a.k.a. Ishikawa or Fishbone)

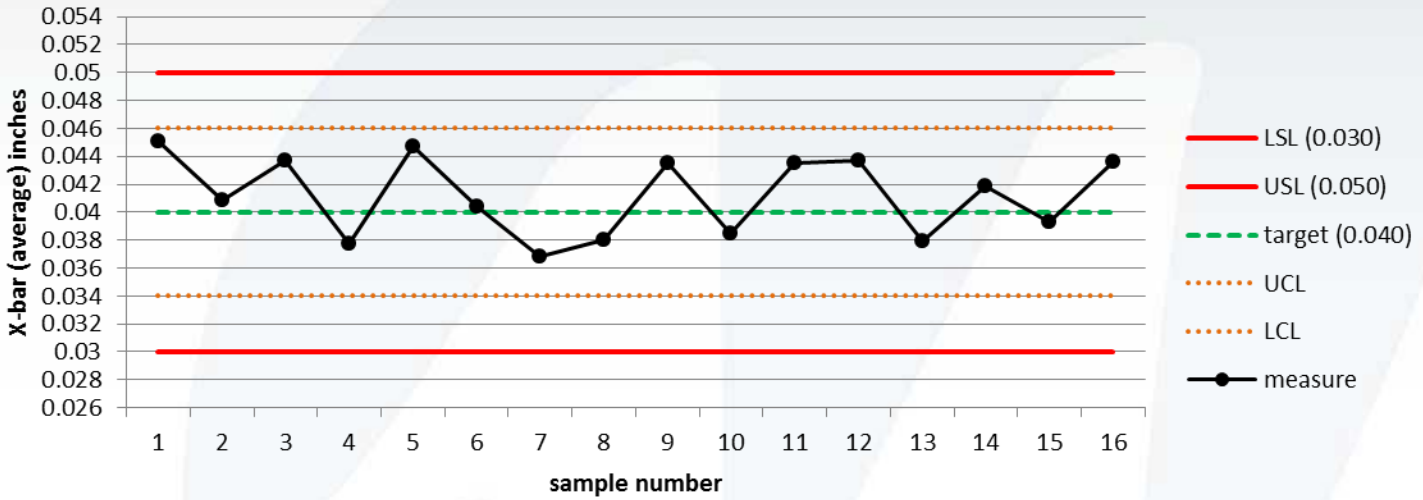
STATISTICAL PROCESS CONTROL (SPC)

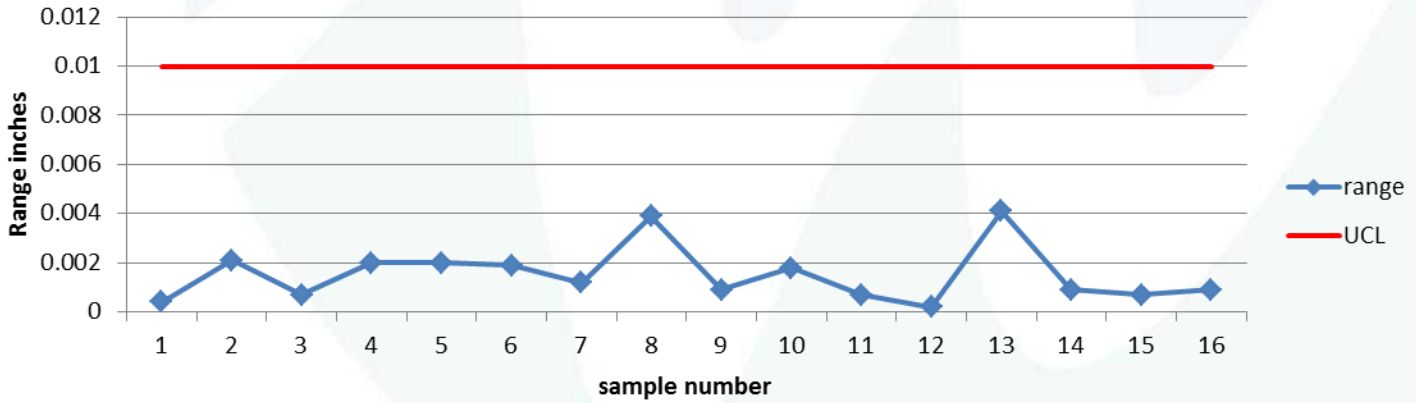
- Measure of process stability or variability

> "… SPC is applied in order to monitor and control a process. Monitoring and controlling the process ensures that it operates at its full potential. At its full potential, the process can make as much conforming product as possible with a minimum (if not an elimination) of waste (rework or scrap)…"
>
> Wikapedia.com

- A process under statistical control is predictable.

SPC: X-Bar / R Charts

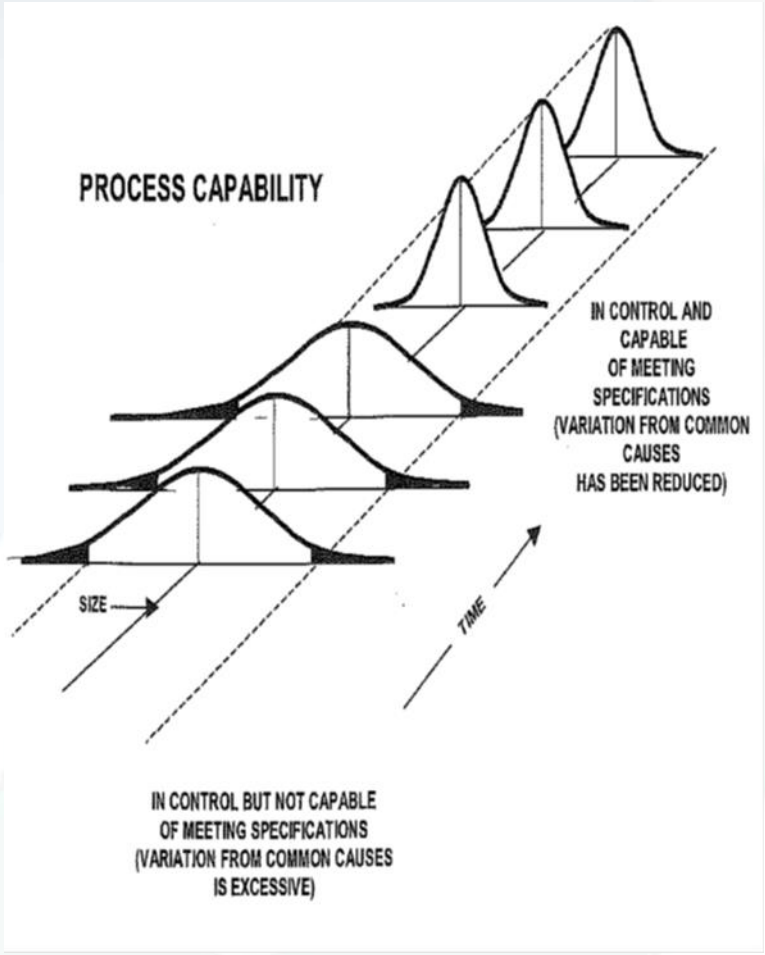




PROCESS MEASURES

- Process Measures
  - Process Performance
  - Process Capability

		Statistical Control	
		In-Control	Out-of-Control
Capability	Acceptable	Case 1	Case 2
	Unacceptable	Case 3	Case 4



INVESTIGATIONS

5W's1H
5Whys
7-Step process
Tools (pareto, cause/effect, etc.)

QUALITY SYSTEMS

- Say what you do (documents)
- Do what you say (training)
- Record what you did (write it down, quality records)
- Check the results (analysis)
- Act on the difference (improvement)

Act on the difference

- Root Cause
  - The fundamental (true) reason a product or process nonconformance occurred.

Act on the difference

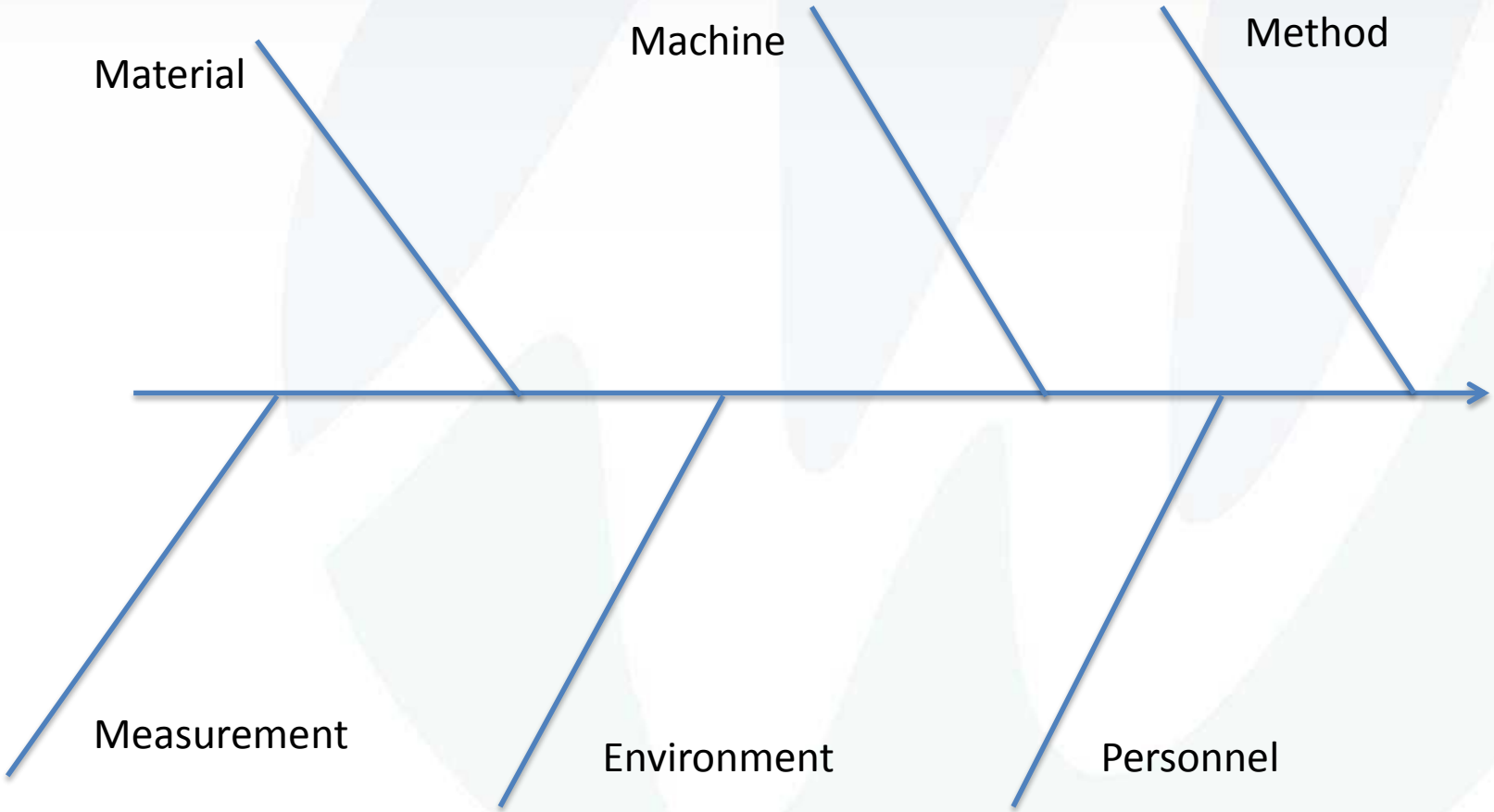
- Root Cause
  - The fundamental (true) reason a product or process nonconformance occurred.
- Root Cause Analysis (RCA)
  - Structured investigation (review) aiming to identify (determine) the true cause of a product or process nonconformance (problem) AND the actions necessary to eliminate it.
    - This extends beyond solving the symptoms of a problem, instead drilling down to discover its most fundamental cause.

Act on the difference

- Root Cause Analysis
  - Get to the root of the problem, not just immediate fix
  - Eliminate recurrence
- Investigative process
  - 5 Whys
  - Who, What, Where, When, Why, How
  - Cause & Effect Diagram

Cause & Effect Diagram

(aka Ishikawa or Fishbone)



METHOD COMPARISON

<table>
<tr><th>Andersen & Fagerhaug</th><th>PDSA</th><th>Six Sigma</th><th>7-Step</th><th>8-Disciplines (8D)</th></tr>
<tr><td></td><td></td><td></td><td>Recognize</td><td></td></tr>
<tr><td>Understand the Problem</td><td rowspan="3">Plan</td><td rowspan="3">Define</td><td rowspan="3">Define</td><td>Plan</td></tr>
<tr><td rowspan="2">Identify Potential Solutions</td><td>Select Team</td></tr>
<tr><td>Define</td></tr>
<tr><td>Data Collection</td><td>Do</td><td>Measure</td><td>Measure</td><td rowspan="2">Determine/ ID / Verify Root Cause & Escape Points</td></tr>
<tr><td>Data Analysis</td><td rowspan="2">Study</td><td>Analyze</td><td>Analyze</td></tr>
<tr><td>Identify Root Cause</td><td>Improve</td><td>Improve</td><td>Choose / Verify Permanent Corrections</td></tr>
<tr><td rowspan="2">Root Cause Elimination</td><td rowspan="2">Act</td><td rowspan="2">Control</td><td>Control</td><td>Validate Corrective Actions</td></tr>
<tr><td>Sustain</td><td>Preventive Actions</td></tr>
<tr><td>Acknowledge Success</td><td></td><td></td><td></td><td>Congratulate Team</td></tr>
</table>

IS – IS NOT MATRIX

Problem Taper length incorrect	IS	IS NOT	Distinction
What happened	*Reported as short*	*Found in retains*	*OOS at customer*
Where it happened	*Reported by customer*	*final inspection data for product lot*	*OOS at customer*
When it happened	*Most recent product lot*	*10 lots shipped in past 8 months*	*No pattern in complaints*
Extent (frequency)	*Reported as every piece inspected*	*No NCRs reported last 16 months First complaint in 24 months*	*No internal pattern*
Who did the inspections	*Unknown inspector*	*multiple inspectors over 16 months*	*New inspector at Customer?*

This was determined to be an inspection issue at the Customer.

BRING IT TO THE CLASSROOM

“Stackable Training for Laboratory Science and Quality Technicians in Biopharmaceutical and Biomedical Manufacturing”

Funded by
National Science Foundation Advanced Technical Education
Award Number: DUE-1304474

Principal Investigator: John Henshaw, PhD,
Dean Workforce Development
Program/Curriculum: Gretchen Ingvason
Sr. Learning Specialist

STACKABLE CURRICULUM

PROGRAM	OVERVIEW	CONTACT TIME		ASQ CERTIFICATION TARGET
Manufacturing Readiness Training – Quality Systems	General QA/QC principles	Non-credit	12 hours	NA
Quality Systems Training	Quality Professional Introduction ISO9001:2008 & FDA GMP Metrology & Inspection Root Cause Analysis Lean Six Sigma	Non-credit	40 hours	Quality Improvement Associate Quality Process Analyst
ALQS Certificate (Analytical Laboratory & Quality Systems)	Core Classes AQS 110 Intro to Quality & Metrology CHE 180 Instrumental Analysis BTC 191 Regulatory & Compliance	Credit	29 credit hours	Quality Inspector
BTDQ Associates Degree (Biotechnology Degree with Quality Concentration)	Biotechnology Degree ALQS Certificate Core and AQS 200 Root Cause Investigation	Credit	65-67 Credit hours	Quality Technician

CODES OF PROFESSIONAL PRACTICE

- Honesty
- Integrity
- Transparency
- Accountability
- Confidentiality
- Objectivity
- Respectfulness
- Obedience to the Law

Teamwork, Communication (verbal/written), Data driven, Ethics - "Do no harm"

BRING TO THE CLASSROOM

- Mathematics
  - Statistic
  - Accuracy / Precision
- Metrology
  - Repeatability / Reproducibility
  - Error analysis
- Documentation Skills
  - Laboratory notebooks
  - Reporting (include failed results)
- Investigation Techniques