QUALITY SYSTEMS in BIOSCIENCE MANUFACTURING

BIOMAN Conference July 2015

Prepared by Gretchen Ingvasen 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
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.
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)
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/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)
<table>
<thead>
<tr>
<th>Title</th>
<th>Section</th>
</tr>
</thead>
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<td>Grants and Agreements</td>
</tr>
<tr>
<td>3</td>
<td>The President</td>
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<td>4</td>
<td>Accounts</td>
</tr>
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<td>5</td>
<td>Administrative Personnel</td>
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<td>Domestic Security</td>
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<td>Aliens and Nationality</td>
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<td>Animals and Animal Products</td>
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<td>Energy</td>
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<td>Federal Elections</td>
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<td>12</td>
<td>Banks and Banking</td>
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<td>13</td>
<td>Business Credit and Assistance</td>
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<td>14</td>
<td>Aeronautics &amp; Space (aka Federal Aviation Regulations)</td>
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<td>Commerce and Foreign Trade</td>
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<td>Commercial Practices</td>
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<td>Commodity and Securities Exchanges</td>
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<td>Housing &amp; Urban Development</td>
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<td>25</td>
<td>Indians</td>
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<td>26</td>
<td>Internal Revenue (aka Treasury Regulations)</td>
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<td>Alcohol, Tobacco &amp; Firearms</td>
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<td>Judicial Administration</td>
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<td>Labor</td>
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<td>Mineral Resources</td>
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<td>Money and Finance: Treasury</td>
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<td>National Defense</td>
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<td>Navigation &amp; Navigable Waters</td>
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<td>34</td>
<td>Education</td>
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<td>35</td>
<td>Reserved (Formerly Panama Canal)</td>
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<td>36</td>
<td>Parks, Forests, and Public Property</td>
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<td>37</td>
<td>Patents, Trademarks, and Copyrights</td>
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<td>38</td>
<td>Pensions, Bonuses &amp; Veterans Relief</td>
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<td>Postal Service</td>
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<td>Protection of Environment</td>
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<td>Public Contacts and Property Management</td>
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<td>Public Health</td>
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<td>Public Lands: Interior</td>
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<td>Emergency Management &amp; Assistance</td>
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<td>45</td>
<td>Public Welfare</td>
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<td>46</td>
<td>Shipping</td>
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<td>47</td>
<td>Telecommunication</td>
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<td>48</td>
<td>Federal Acquisition Regulations</td>
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<td>49</td>
<td>Transportation</td>
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<td>50</td>
<td>Wildlife &amp; Fisheries</td>
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</tbody>
</table>
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 ...
...” (Wikipedia.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
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
Measurement Equipment
Meet Specification
Ship Product
Inspection Process
Yes
No
Measurement Complete
Product Specification
Part Drawing
Etc.
Sort / Rework
Non-Conforming Product
Material Review Board (MRB)
Downgrade Product
Scrap Product
Meet Specification
Yes
Ship Product
No
Sort / Rework
Non-Conforming Product
Material Review Board (MRB)
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
• 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)
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)
HISTOGRAM EXAMPLE
SCATTER PLOT (DIAGRAM)

- None
- 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)...”

• A process under statistical control is **predictable**.
SPC: X-Bar / R Charts

![X-bar chart](image)

![Range chart](image)

- Lower Specification Limit (LSL) (0.030)
- Upper Specification Limit (USL) (0.050)
- Target (0.040)
- UCL (Upper Control Limit)
- LCL (Lower Control Limit)
- Measure

Sample number:

7/6/2015

BIOMAN Conference
• Process Measures
  – Process Performance
  – Process Capability
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
  – Cause & Effect Diagram
Cause & Effect Diagram
(aka Ishikawa or Fishbone)

- Material
- Machine
- Method
- Measurement
- Environment
- Personnel
<table>
<thead>
<tr>
<th>Andersen &amp; Fagerhaug</th>
<th>PDSA</th>
<th>Six Sigma</th>
<th>7-Step</th>
<th>8-Disciplines (8D)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Understand the Problem</td>
<td>Plan</td>
<td>Define</td>
<td>Define</td>
<td>Recognize</td>
</tr>
<tr>
<td>Identify Potential Solutions</td>
<td></td>
<td></td>
<td></td>
<td>Plan</td>
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<td></td>
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<td></td>
<td></td>
<td>Select Team</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Define</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Interim Containment &amp; Actions</td>
</tr>
<tr>
<td>Data Collection</td>
<td>Do</td>
<td>Measure</td>
<td>Measure</td>
<td>Determine / ID / Verify Root Cause &amp; Escape Points</td>
</tr>
<tr>
<td>Data Analysis</td>
<td>Study</td>
<td>Analyze</td>
<td>Analyze</td>
<td>Choose / Verify Permanent Corrections</td>
</tr>
<tr>
<td>Identify Root Cause</td>
<td></td>
<td></td>
<td></td>
<td>Validate Corrective Actions</td>
</tr>
<tr>
<td>Root Cause Elimination</td>
<td>Act</td>
<td>Control</td>
<td>Control</td>
<td>Preventive Actions</td>
</tr>
<tr>
<td>Acknowledge Success</td>
<td></td>
<td></td>
<td></td>
<td>Congratulate Team</td>
</tr>
</tbody>
</table>
**IS – IS NOT MATRIX**

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

*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

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