Why is Cozzoli concerned about Validation?
- Market Equipment as cGMP
- Customer Satisfaction
- Reputation
- Repeat Business

Why should you be concerned about Validation? You client will expect you to be knowledgeable about Pharmaceutical requirements.
- Equipment Requirements
- FDA Expectations
- cGMP Requirements
- Validation Documentation
- Validation Support

What is the Terminology?

Agencies:
- FDA - Food & Drug Administration
  - CBER - Center for Biological Evaluation & Research
  - CDER - Center for Drug Evaluation & Research
- WHO - World Health Organization - publishes good practices for the manufacture and quality control of drugs
- MCA - Medicines Control Agency - British Regulatory Agency - Publishes rules and guidance for Pharmaceutical Manufacturers and Distributors.
- EN - European Committee for Standardization - publish standards

Regulations:
- CFR - Code of Federal Regulations
  - 21 CFR Parts 210 & 211 - current good manufacturing practice for the manufacture, processing, packing, or holding of drugs.
  - cGMP - Current Good Manufacturing Practices
- USP 24 NF 19 - U.S. Pharmacopeia & National Formulary - The Official Compendia of Standards
  - USP 24 <1211> Sterilization and Sterility Assurance / General Information
  - USP 24 <85> Biological Tests / Bacterial Endotoxin Test
Commonly Used Terminology:

CFU - Colony Forming Units - Indication of Viable organisms in an air or product sample.

Log Reduction - Reduction in Endotoxin or Biological Indicator during depyrogenation, sterilization, or sanitization. For example 6,000,000 CFU/mL $6 \times 10^6$ are injected into a vial and depyrogenated. After depyrogenation the vial is tested. The results are $<10,000$ CFU/mL ($<1 \times 10^4$) a 3-Log reduction is obtained if $<10$ CFU/mL a 6-log reduction has been obtained.

Endotoxin - A Toxin produced within a microorganism and released upon destruction or reproduction of the cell in which it is produced.

- CSE - Control Standard Endotoxin
- Pyrogen - A substance that produces fever. Endotoxins are pyrogens.

Media - Liquid product that will support the growth of microorganisms. This test is used on filling machines to determine if the equipment results in sterile fills.

Sterile - Free from bacterial or other microorganisms. Note: An article such as a vial can be sterile but still have pyrogens.

Aseptic - The state of being free of pathogenic organisms - i.e. Bacteria, mold and spores.

Aseptic Core - This area requires special gowning and is virtually free from microorganisms.

Parenteral - Medication taken into the body or administered in a manner other than through the digestive tract, as by intravenous (IV) or intramuscular (IM) injection.

Fill Room - Room where vials are filled with the drug product. Fillers and Trayloaders can be found in this area.

Washroom - Room where vials are batch washed, loaded into trays or continuously washed and delivered into a Depyrogenation Tunnel.

Class 100,000 - Production area where particulate counts cannot exceed 100,000 Particulate per cu.ft. of 0.5 (u) or larger sized particles. ($<100$ CFU)

Class 10,000 - Production area where particulate counts cannot exceed 10,000 Particulate per cu.ft of 0.5(u) or larger sized particules ($<20$ CFU). (0.05" WC Required Between Classifications).

Class 100 - Production area where particulate counts cannot exceed 100 Particulate per cu.ft. of 0.5(u) or larger sized particles. ($<3$ CFU). (SD-throughout entire cycle).

HEPA Filter - Filters that remove $\geq 99.97\%$ (397, 4-9's) of particulates, size 0.3(u) or larger. Filter integrity tested at ambient temperature. Despatch does not recommend challenge materials be used, such as DOP (Emery 3004).

Wrap - The plastic, shrink wrapped vials. Also called “flat” and "shrink"

SOP - Standard Operating Procedures

Software Life Cycle - Method used to develop and track changes to software.

Dead Code - Programming code that is not used, but is left in the programming.
What is Validation?

Validation is establishing documented evidence which provides a high degree of assurance that a specific process will consistently produce a product meeting its pre-determined specifications and quality attributes.

(Guideline on General Principles of Process Validation - May, 1987)

Prepared by
Center for Drug Evaluation and Research
Center for Biologics Evaluation and Research
Center for Devices and Radiological Health
Food and Drug Administration (ref: www.fda.gov)

Why Perform Validation? IT’S THE LAW

483 - Written Observation

Warning Letter - Written communication from FDA

Shut Down - Law Enforcement Agency "padlocks" the facility. No product can be sold. Requires a Civil Trial.

Consent Decree - Agreement through the civil court system, whereby the government and company agree to an injunction, but company does not admit guilt.

Who Performs Validation?
1. Pharmaceutical Company
   Engineering Department
   Validation Department
2. Third Party Consultant
3. Equipment Manufacturer
INSTALLATION QUALIFICATION

Installation Qualification Protocol - Referred to as an "IQ"

Used to document that the unit is installed properly and meets the requirements of cGMP, client specifications and manufacturers specifications. Verification included are:

- Equipment/Control System/Software Checklists
- Documentation SOP's required for testing
  - Operating Manuals
  - Vendor Cut Sheet
  - Certifications
    - Material of Construction (Mill Reports)
    - Certification for Individual Components
    - Certificate of No Dead Code
  - Drawings are reviewed and components verified
  - Required utilities are verified against actual utilities

OPERATIONAL QUALIFICATION

Operational Qualification Protocol - Referred to as an "OQ"

Used to document that the unit is functioning properly. Includes verification/testing as follows:

- Instrument Calibrations - Process and Test
- SOP's required for testing
- Operator Interface (If Applicable)
- Manual and Automatic Controls
- PLC Logic / Sequence of Operation
- Alarms
- Unit Operation

PERFORMACE QUALIFICATION PROTOCOL

Performance qualification protocol - Referred to as a "PQ"

Used to document the unit and or process is performing as required by regulatory standards. Most critical document of the validation protocols. Includes verification / testing as follows:

- Instrument Calibrations - Process and Test
- SOP's required for testing
- Performance Testing
  - Media Fills
  - Particulate Challenges
  - Seal Integrity
IQ/OQ VALIDATION PROTOCOL - WRITTEN

Installation Qualification and Operation Qualification written protocol that can be used as part of the validation effort for a production line. Upon successful execution of the protocols the results can be used to substantiate validation efforts with confidence that the equipment as installed performs as intended and does not perform unintended behavior.

FACTORY ACCEPTANCE TEST PROTOCOL - WRITTEN

Factory acceptance written test protocol includes a list of tests and checks providing an acceptable degree of confidence that the equipment built fits the original specifications.

PQ / PERFORMANCE QUALIFICATION PROTOCOL - WRITTEN

Performance Qualification written protocol that can be used as part of the validation effort for a production line. Upon successful execution of the protocols the results can be used to substantiate validation efforts with confidence that the equipment as installed performs as intended and does not perform unintended behavior.

IQ/OQ VALIDATION PROTOCOL EXECUTION

(PER DIEM) Available upon Request

FACTORY ACCEPTANCE TEST PROTOCOL EXECUTION (PER DIEM) Available upon Request