Quality Assurance

Northeast Biomanufacturing Center and Collaborative

Chapter Objectives

- Define the term *quality* as it relates to the biopharmaceutical manufacturing industry

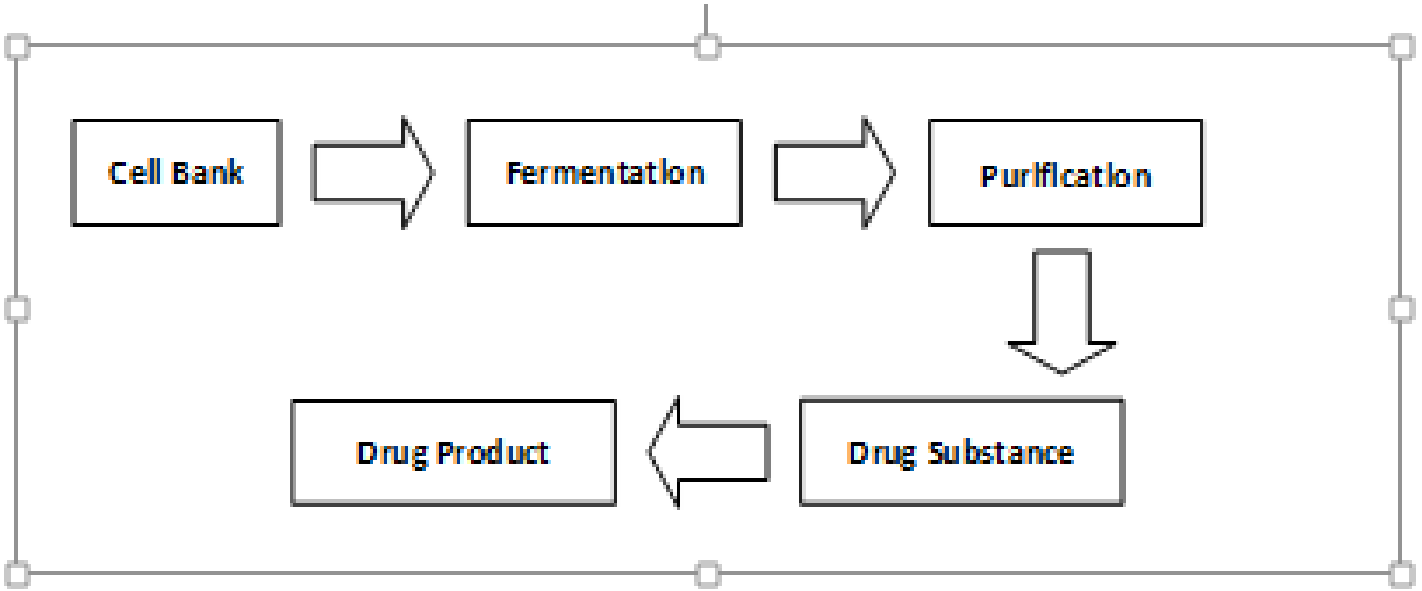
- Define and distinguish between the terms *quality assurance* and *quality control* and explain how they both fit within a quality system in the industry.
- Define the roles of the organizational groups quality assurance, quality control, and regulatory affairs

- Describe the specific functions of the QA organizational group.
- Describe the basis of the key regulations and the key global regulatory agencies (FDA and EMA) overseeing operations

- Define the terms *GMP* and *cGMP* and their place in a QA system.
- Analyze a situation where a QA failure in the pharmaceutical industry resulted in significant public impact

Quality Assurance – Biopharmaceutical Production

In the manufacture of biopharmaceuticals, both drug substances and drug products are produced



Biopharmaceutical production process

Drug Substance vs Drug Product

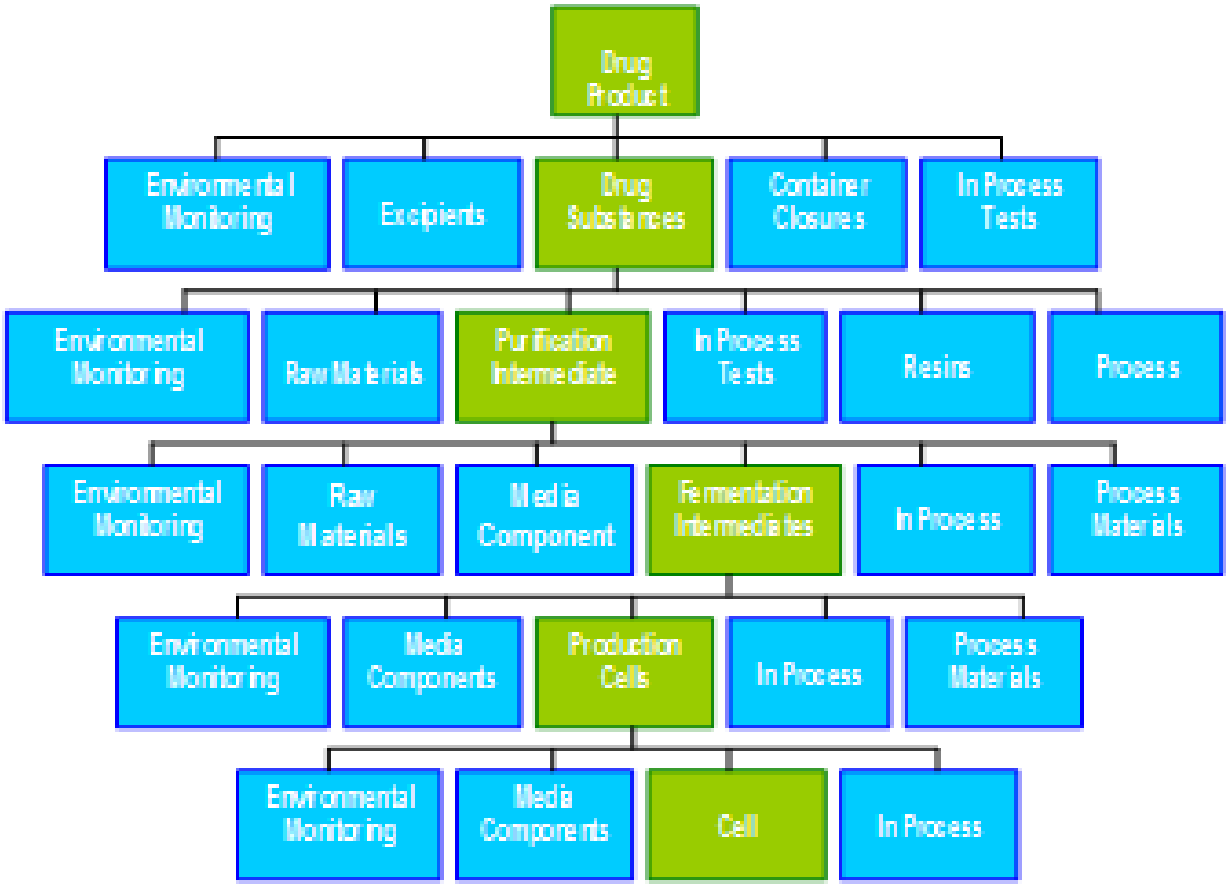
- **Drug substance** – any substance or mixture of substances intended for use in the manufacture of a drug product and when used so becomes an active ingredient of the drug product—provides the therapeutic effect in the product

- **Drug product** - a formulated dosage form that contains the drug substance, normally (but not always) in combination with one or more inactive ingredients (excipients), that is ultimately used by the patient

Specifications

To ensure the quality of each batch of drug product, all of the materials and processing steps from the establishment of the cell bank through cell culture/fermentation, purification, and final drug product manufacture, must be shown to be in compliance with expected standards and **specifications**

Biopharmaceutical QC Testing Scheme



Quality

- Safety and effectiveness of the product is the primary concern
  - Safe – product will not bring about unexpected adverse effects
  - Effective – alleviate symptoms and/or prevent illness
  - Pure – composition of the product must be precisely known and not contain unexpected impurities or expected impurities in a greater than permissible concentration

Quality Assurance (QA)

- Quality Assurance refers to the activities undertaken to guarantee that an organization produces a product of expected and stated quality

- QA, required by law, oversees operations and procedures to guarantee that components used in the manufacture of products and the final products themselves meet the required quality standard

Quality Control (QC)

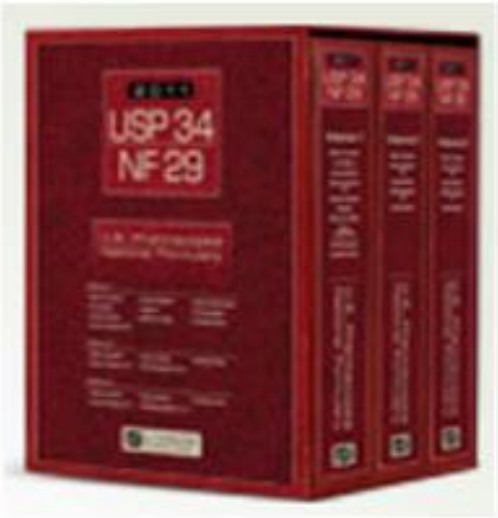
Often used in two contexts:

- efforts taken to test both the components that go into making a product and the final product itself to ensure that requisite standards are met
- an organizational group that is often under the direction of the QA group; the QC group is responsible for performing actual tests and/or measurements on product samples and drawing conclusions about the properties of the entire batch of product from which the sample was taken

Pharmacopeia Standards

A publication that describes the standards for medicines and their active substances

- Earliest known is from China and dates back to 4000 B.C.E.
- Several available today
  - **United States Pharmacopeia (USP)**
  - **European Pharmacopeia (PhEur)**
  - **Japanese Pharmacopeia (JP)**



United States Pharmacopeia and the National Formulary- USP NF

Quality Systems (QS)

Defined as “a management system to direct and control a pharmaceutical company with regard to quality.”

- It is not only a way of thinking about quality issues but also a “management system” that defines how management expends its time and energies in the QS arena
- QC and QA are seen as parts within a Quality System (QS); those who work in QC typically report to a manager who in turn reports to a QA leader.

Good Manufacturing Practices (GMPs)

a set of guidelines that describe general principles that must be complied with in the production and testing of pharmaceutical products to ensure that those products will be safe and effective

Good Manufacturing Practices

There are two widely referenced sets of GMPs that are used globally:

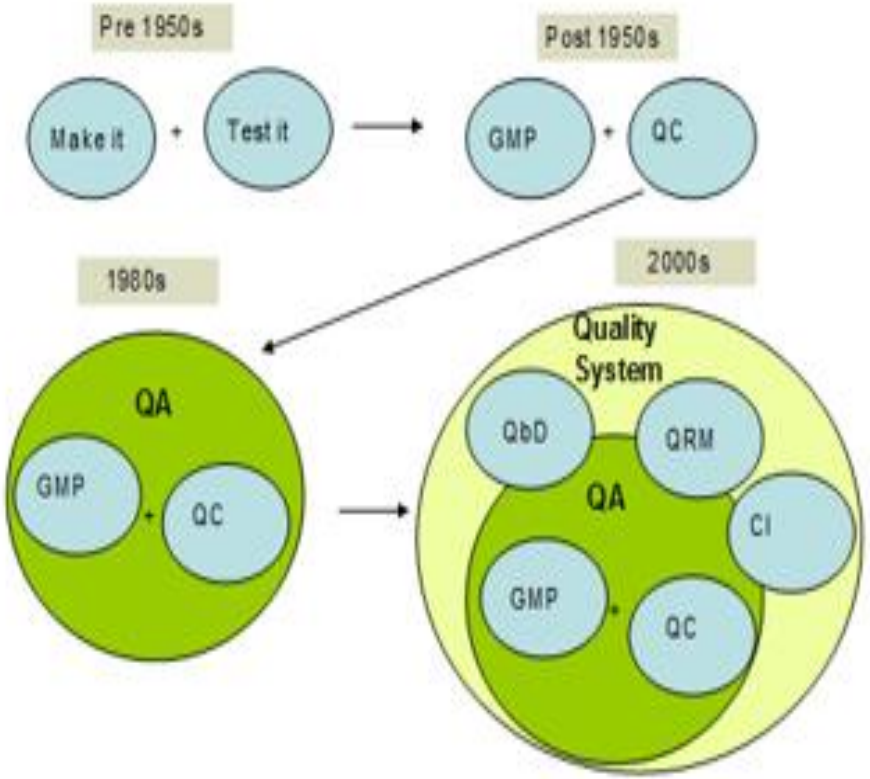
- the United States cGMP, which is enforced by the FDA and applies to all products produced within the United States (including Puerto Rico) as well as all imported products
- the European Union (EU) GMP

United States GMP vs European GMP

CFR Sub Part #	Topic	EU Vol. 4 Chapter	Topic
A	General Provisions	1	Quality Management
B	Organization and Personnel	2	Personnel
C	Buildings and Facilities	3	Premises and Equipment
F	Production and Process Controls	5	Production
I	Laboratory Controls	6	QC
J	Records and Reports	4	Documentation
K	Returned and Salvaged Drug Products	8	Complaints & Product Recall

Quality System- Key Quality Processes

- Key qualities:
  - Quality by Design (QbD)
  - Quality Risk Management (QRM)
  - Continuous Improvement (CI)



Elements of a Pharmaceutical Quality System

- **Quality by Design (QbD)**:
  - QbD is concerned with the product being designed with the ultimate quality/performance characteristics in mind from the outset
- **Quality Risk Management (QRM)**:
  - a systematic process for the assessment, control, communication, and review of risks to the quality of the drug (medicinal) product across the product lifecycle. QRM describes methodologies to deal with risk management
- **Continuous Improvement (CI)**:
  - Recognizing that all products, processes, and systems can be improved, CI describes methodologies and management systems to enable ongoing improvement**.**

Testing Characteristics Table

Characteristic	Function	Test Performed
potency	biological activity immunological activity chemical activity	bioassay ELISA HPLC
purity	chemical biochemical process materials	residual DNA
identity	characterization methods	chromatography electrophoresis
safety	microbiological	sterility endotoxin bioburden viral tests

Quality Unit

- Functional group responsible for overseeing the execution of activities in compliance with cGMP
- Act independently of production/manufacturing in executing its responsibilities
- Includes Quality Control and Quality Assurance functions
  - **Quality Control** involves inspection and testing
  - **Quality Assurance** assures product integrity, potency, purity, and stability of all aspects that influence product quality throughout the lifecycle of the product.

Primary QA Activities

Documentation Review

- Product documentation
- Test Record
- Investigation Reports
- Change Control
- Marketing Authorization
- Deviations

Documentation Review

- Product Document
  - reviews calculations for correctness; inputted materials to ensure the right starting materials are utilized; and that in-process data (such as tablet hardness and weight for a pharmaceutical product or volume of fill for a liquid biological product) are within specifications
  - QA assures that all deviations are appropriately investigated for potential product impact

Documentation Review-Error Types

Table 7-3. Types of errors that result in poor quality

Types of errors	Potential result
transcription errors	incorrect use of data in downstream processing
omission of data, such as weights	loss of the production batch for missing critical parameters
omission of details, such as conditions during deviations	loss of the production batch for missing critical details to support the quality of the batch
omission of verification, such as forgetting to document the witness of a critical step	loss of the production batch for critical processing steps
mix-up of labeling, such as the wrong label used	cross contamination of the batch with incorrect materials
skipping of processing steps, such as not paying attention to each step of the process	loss of the production batch or possible contamination of the batch

Test Records

- once a product has been manufactured it must be tested to ensure it meets the specifications for safety, purity, efficacy, and quality
- test record review ensures that the product has met parameters that are important relative to the product quality. Any results that are outside of the specification or trending negatively (away from a specification) must be investigated.

Drug Product -Certificate of Analysis

Drug Product - Insulin for Human Injection – USP		
Test	**Specification**	**Results**
identification	part A – clear colorless solution part B – HPLC retention time matches the reference standard	clear colorless solution – Pass Pass
bacterial endotoxins	< 80 USP endotoxin units/100 insulin units	< 5 EU/100 insulin units – Pass
sterility	meets USP <71> sterility requirements	Pass
pH	between 7.0 – 7.8	7.6 – Pass
assay	95.0 – 105.0 % label claim	101.3% - Pass

Drug Substance -Certificate of Analysis

Drug Substance - Insulin lispro DS – USP		
Test	**Specification**	**Results**
identification	part A – chromatogram part B – peptide fragments	Pass Pass
loss on drying	not more than 10.0% @105°C for 16 hrs	5% – Pass
limit of high molecular weight proteins	not more than 0.25%	0.1% – Pass
zinc content	between 0.30 and 0.60% found	0.40% – Pass
assay	TBD	

Investigation Reports

Unusual findings in the production, documentation, or test records must be fully investigated. Investigation should include:

- description of the event (or deviation), background
- determination of the root cause
- negative trends
- indicated Corrective Actions and Preventative Actions (CAPA) and a conclusion regarding the event
- QA review of the final investigation report and ensure it is adequate and proportionate to the seriousness of the deviation.

Change Control

- formal process by which an organization documents changes to a process, procedure, or other element of operations

- All elements that might conceivably impact the product quality (whether directly or indirectly) should be subject to change control.

Marketing Authorization

- European term for the license that allows a company to market a medicine in either some or all of the countries in the European Union.
- also used to refer to the set of documents that is submitted to the regulatory agency to obtain that license
- The QA team must ensure that individual batches of the product are manufactured in the manner that is described in the Marketing Authorization

Deviations

- If a deviation occurs and there is a potential to impact product that has already been released to the market, there are several actions that must be considered
- In the most significant cases products are recalled from the market, often at great expense and to the dismay of executives, partnering companies, stockholders, and investors

Recall Classifcations

- **Class I**: dangerous or defective products that predictably could cause serious health problems or death (e.g. injectable drug determined to be contaminated, a label mix-up on a lifesaving drug)

- **Class II:** products that might cause a temporary health problem or pose only a slight threat of a serious nature (e.g. a drug that is under-strength but is not used to treat life threatening situations)

- **Class III:** products that are unlikely to cause any adverse halth reaction but violate FDA labeling or manufacturing laws (e.g. A minor container defect, lack of labeling on the product container)

Documentation in Pharmaceutical Manufacturing

Two main reasons why proper documentation is so vital to the industry:

- prevents the errors and misunderstandings that arise with spoken communication
- provides a definitive record of occurrences at a particular time during the manufacture of a particular batch of product

Proper Documentation

- Prepared at the time the actions occur
- Actions must be recorded using permanent means
- Appropriate parties must sign off on initial documentation
- For critical steps, an independent person must verify what is being documented

Types of Documentations

- production document (steps of the manufacturing operation)
- operational log books (documentation of cleaning or other critical steps)
- training documents

Electronic Documentation

- electronic format can include any combination of text, graphic, data, audio, pictorial, or other information represented in digital form that is created, modified, maintained, archived, retrieved, or distributed by a computer system

- electronic documents require additional controls to prevent the documents from being changed or altered.

Regulations and Regulatory Agencies

- regulations for biologicals have paralleled the development of the cGMP and are defined in CFR (21 CFR 600-800)
- In the United States these requirements are published in the Code of Federal Regulations.
- Documentation requirements include information on clinical and product development as well as product manufacturing information such as:
    - facilities
    - materials
    - methods
    - procedures
    - processes
    - controls

Regulatory Inspections

- The purpose of these inspections is to verify that activities are being performed in accordance with cGMP requirements and with the requirements of the dossier(s) that the organization submitted to the relevant agency
- typically lasts for approximately a week or more with 2–3 inspectors visiting the site

Regulatory Inspections Contd

- inspection begins with a presentation of the site and its activities, key products, etc., to the inspection team by the senior management

- inspection team will then tour the facility and observe events as they occur in routine operations

Types of Regulatory inspections

- Pre-approval inspection: performed at the time the dossier is under review for licensing
- Routine inspection: performed as surveillance of ongoing compliance with cGMP using a prescribed schedule based on the regulatory agency's requirements
- For cause inspection: can be performed when the regulatory agency has concerns over the manufacturing and control of a product/products

Frequency of Regulatory Inspections

Pre-approval :

- each Biological License Application (BLA)
- new products, new facilities or major renovations

Routine:

- Annually, bi-annually, or less frequently than every two years
- Risk based
- More frequent for sole supply, vaccines, or parenteral products
- Usually unannounced

For Cause:

- As events dictates
- Unannounced and compliance experts involved

Documents Reviewed

- facility and system drawings
- validation and qualification reports and data
- laboratory data
- SOPs
- production batch records
- engineering and maintenance records
- training records
- investigation reports
- change controls
- organizational charts

Regulatory Inspections- Close Out Meeting

- At the end of the inspection the team will typically provide the site management with an indication of the deficiencies observed during their inspection in a close-out meeting.
- For the FDA this list of deficiencies is provided as an official FDA form, FD 483 [often referred to as a 483]

Response to Regulatory Inspections

- The organization then begins the process of responding to the team's findings with appropriate actions
- These actions are later submitted to the regulatory agency, and the agency can either accept them or require further action and/or dialog

Sanctions

- If the findings are minor or the organization addressed them appropriately, the FDA then considers the site as Voluntary Actions Indicated (VAI).
- If the site has not made the appropriate corrections or if systemic issues continue over successive inspections, the facility may be considered Official Actions Indicated (OAI).

Sanctions Cont'd

- In the case of OAI, there are a number of options the agency can take.
  - It can issue a warning letter, which is considered a serious communication and indicates the site remains deficient—this can result in sanctions.
  - Other actions can include seizure of products, issuance of a Consent Decree, or closure of a facility