Quality by Design (QbD) & Process Analytical Technology (PAT)

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What is Quality by Design (QbD)?

QbD is:

- A Quality System for managing a product's lifecycle
- A regulatory expectation
- Intended to increase process and product
- understanding and thereby decrease patient risk
- A multifunctional exercise

QbD services QbD is a new approach for R&D and can be a means to drastic time-to-market cutback, faster process knowledge and speeding up the development process.

Principle QbD Concepts:

- Risk and knowledge based decisions
- Systematic approaches process development
- Continuous Improvement
- This leads to “capable” processes

QbD Current approach:

- Quality is assured by testing and inspection.
- It includes only data intensive submission which includes disjointed information without “big picture”.

Current approach…

- Here, any specifications are based on batch history.
- Here there is “Frozen process,” which always discourages changes.
- It focuses on reproducibility which often avoids or ignores variation.

Advantages of Adopting Quality by Design Approach

For industry

a) It helps in better understanding of the process.

b) It reduces batch failure.

c) It ensures better design of products with fewer problems in manufacturing.

d) It allows for continuous improvement in products & manufacturing process.

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For FDA

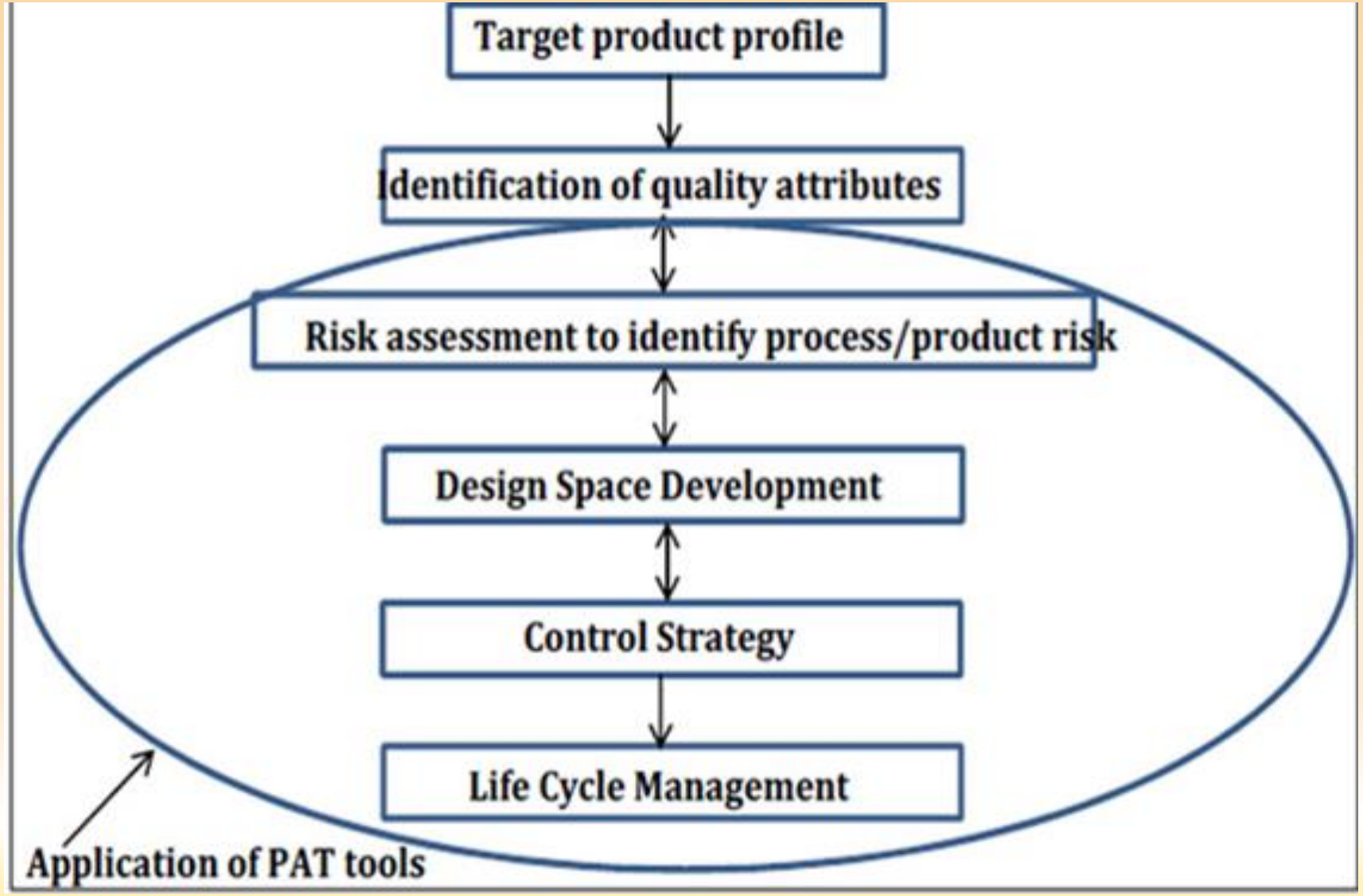
a) It enhances scientific base for analysis.

b) It provides better consistency.

c) It provides more flexibility in decision making.

d) It ensures decisions are made on scientific base & not on observed information.

Elements of Quality by Design



Quality Target Product Profile (QTPP)

Necessary Elements

- Quality characteristics: sterility, purity etc. (including specific safety-related impurities where necessary)
- Pharmacokinetic characteristics: dissolution etc.
- Therapeutic effect
- Target patient population: neonate, adult etc., clinical diagnosis
- Shelf life: temperature, light conditions etc.

Desired Elements

- Dosage form: liquid for injection, solid tablet etc.
- Route of administration: oral, IV, IM, SC
- Clinical setting: self or clinic administration
- Primary/secondary packaging: glass or plastic vial/syringe; blister packaging etc

Other Elements as Appropriate

Critical Quality Attribute (CQA)

Critical Quality Attribute (ICH Q8):

"A property or characteristic that when controlled within a defined limit, range, or distribution ensures the desired product quality."

- Potential CQAs are derived from the QTPP and guide product and process development.
- CQAs are identified by quality risk management and experimentation to determine the effect of variation on product quality.
- The CQA list can be dynamic and may be updated based on product and process knowledge.

Critical Process Parameters (CPP)

Critical process parameters (CPPs) are defined as “parameters whose variability have an impact on a CQA and therefore should be monitored or controlled to ensure the process produces the desired quality” Process robustness is the ability of a process to demonstrate acceptable quality and performance and tolerate variability in inputs at the same time.

Process capability is a statistical measure of the inherent process variability for a given characteristics. The most widely accepted formula for process capability is six-sigma . Process capability index is the value of the tolerance specified for a particular characteristic divided by the process capability, which is defined as follows…

$$\textit{Process capability index (CpK)} = \frac{\textit{Upper limit of specification - Lower limit of specification}}{\text{6-Standard deviation}}$$

If the CpK is significantly greater than one, the process is defined capable. But if the process capability is low, there are five step procedures to progressively reduce the variability of the process. These five steps are:

I. Define: The intended improvement should be clearly stated

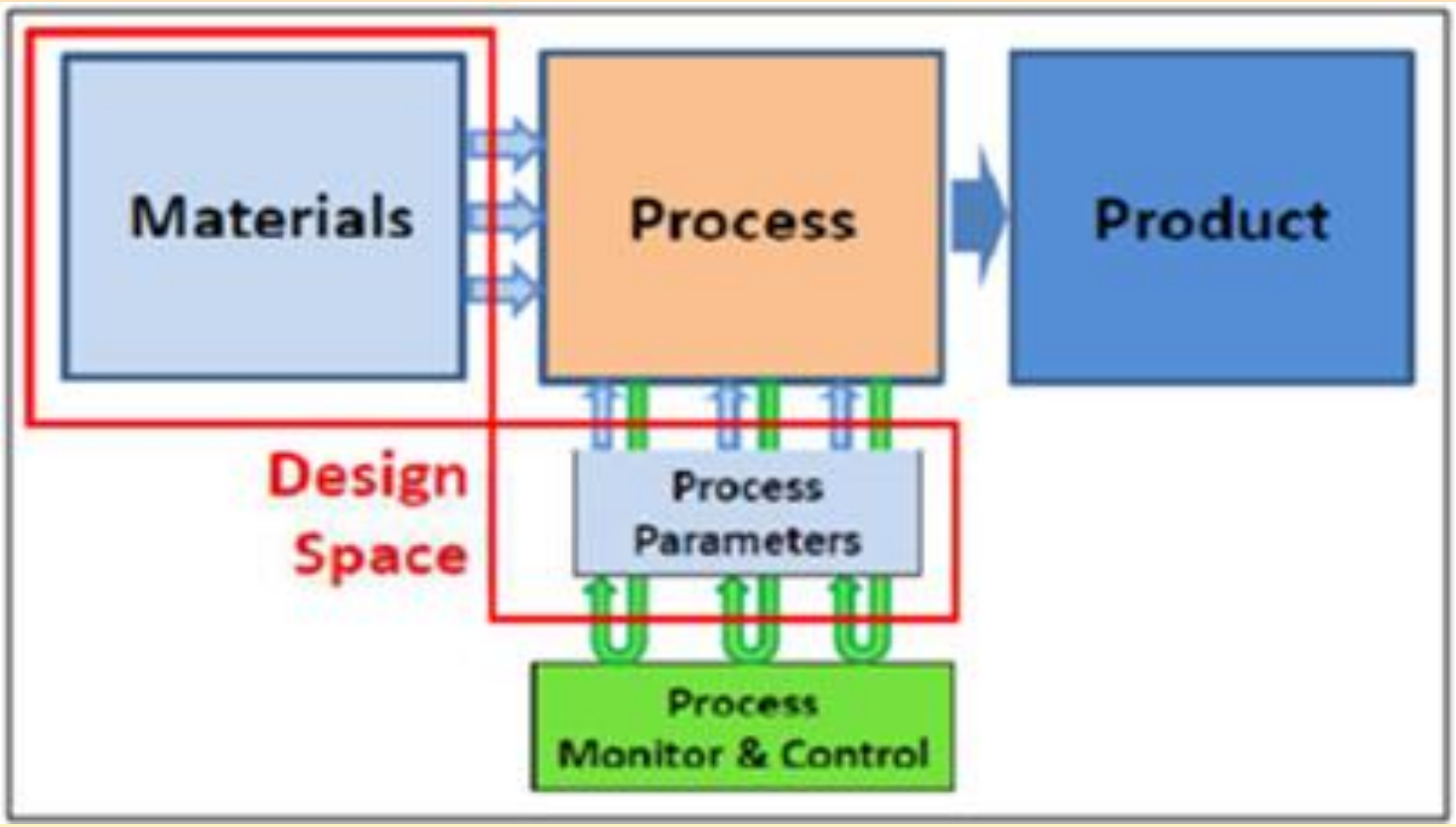
II. Measure: The critical product performance attributes should be measured to see if they are out of specification and used to the sigma level of the process.

III. Analyze: When the sigma level is below the target, steps should be taken to increase it, starting by identifying the most significant causes of the excessive variability.

IV. Improve: The process should be redesigned and/ or process controls should be incorporated to eliminate or attenuate the significant toot causes of variance.

V. Control: The improved manufacturing process should be evaluated and maintained.

Design space



Design Space

- ICH Q8 (R2) defines Design space as, the multidimensional combination and interaction of input variables (e.g. material attributes) and process parameters that have been demonstrated for provide assurance of quality. It will Working within the Design space is not be considered as a change, Movement out of the Design space it is considered to be a change and would normally initiate a regulatory post-approval change process.
- Design space is proposed by the applicant and is subject to regulatory assessment and approval. Thus Design space is potentially scale and equipment dependent, the Design space determined at the laboratory scale may not be relevant to the process at the commercial scale.

Risk Assessment

Risk assessment is the linkages between material attributes & process parameters. It is performed during the lifecycle of the product to identify the critical material attributes & critical process parameters. A material attributes can be an excipients raw material, drug substances, reagents, solvents, packaging & labelling materials. A material attributes can be quantified & typically fixed but sometimes can be changed during further processing .

E.g. Impurity profile, porosity, specific volume, sterility.

PROCESS ANALYTICAL TECHNOLOGY (PAT)

- The concept originates from the desire of the regulators to shift control of product quality towards a science-based approach that explicitly attempts to reduce the risk to patients by controlling the manufacturing based on understanding of the process

From a PAT standpoint, a process is considered well understood when:

a. All critical sources of variability are identified and explained;

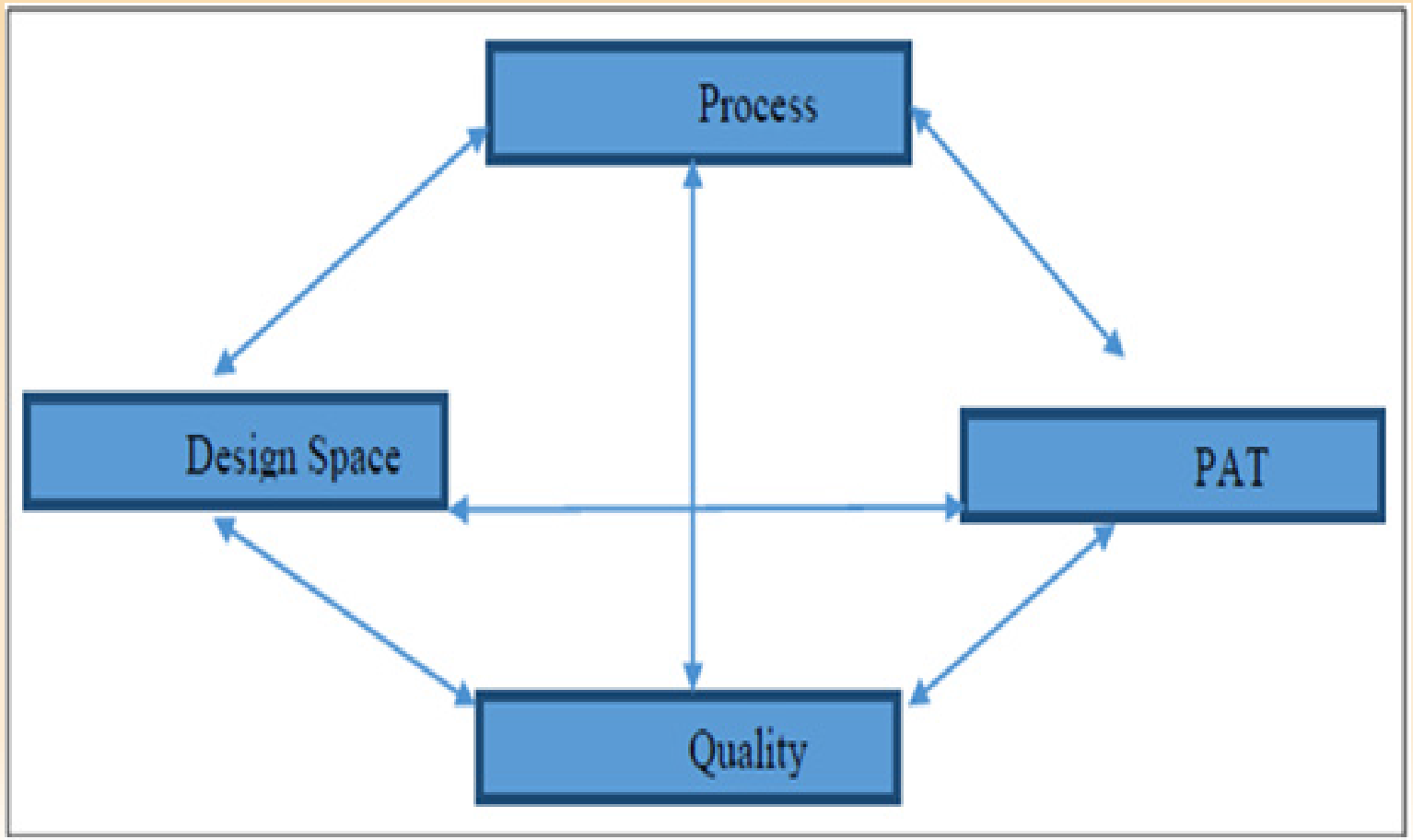
b. Variability is managed by the process; and

c. Product quality attributes can be accurately and reliably predicted

PAT has been defined as “A system for designing, analyzing, and controlling manufacturing through measurements, during processing of critical quality and performance attributes of raw and in-process materials and processes, with the goal of ensuring final product quality”.

The goal of PAT is to “enhance understanding and control the manufacturing process, which is consistent with our current drug quality system: quality cannot be tested into products; it should be built-in or should be by design.”

Interrelationships between PAT and QbD



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QUALITY BY DESIGN
FDA INITIATIE ON PROCESS ANALYTICAL TECHNOLOGY(PAT)
PAT GUIDANCE ,STANDARDS AND REQULATORTY REQUIREMENT

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Introduction to QbD:

Quality by design(QbD) is a quality for managing a product's lifecycle which is emerging to enhance the assurance of safe and Effective drug supply to the consumer, and also offers promise to significantly improve manufacturing quality performance.

The quality of the pharmaceutical product can be evaluated by in vivo or vitro performance tests. QbD provides assures of in vitro product performance and in vitro product performance provides assurance of in vivo product performance. "hence QbD relate to product performance".

➢QUALITY

The suitability of either a drug substance or a drug product for its intended use. This term includes such attributes as the identity, strength and purity. Pharmaceutical quality refers to product free of contamination and reproducibly delivers the therapeutic benefit promised in the label to the consumer.

➢QUALITY BY DESIGN

A systematic approach to development that begins with predefined objectives and emphasizes product and process under standing and process control, based on sound science and quality rick management

Principle of Qbd Concepts

- Risk and knowledge based decisions
- Systematic approaches for process development
- Continuous improvement
- This leads to capable processes

Significance Of Qbd

- Qbd is good business
- Eliminate batch failures
- Minimize deviations and costly investigations
- Avoid regulatory compliance problems
- Organizational learning is an investment in the future
- Qbd is good science
- Better development decisions
- Empowerment of technical staff opportunities
- Efficient, agile, flexible system
- Increase manufacturing efficiency, reduce costs and
- Project rejections and waste
- Build scientific knowledge base for all products
- Better interact with industry on science issues

Steps Involved In Quality By Design Products

1. Development of new molecular entity
    a) Preclinical study
    b) Nonclinical study
    c) Clinical Study
    d) Scale up
    e) Submission for market Approval
2. Manufacturing
    a) Design Space
    b) Process Analytical Technology
    c) Real time Quality Control

3. Control Strategy

a) Risk based decision

b) Continuous Improvement

c) Product performance

Seven steps of quality by design start up plan

1. Hire an independent Quality by design expert.
2. Audit your organization and process with the expert conducting a gape analysis.
3. Hold a basic quality by design workshop with all your personal.
4. Review the expert’s report and recommendation.
5. Draft an implementation plan, timelines and estimated costs.
6. Assign the resources (or contract out).
7. Retain the independent expert as your “Project Assurance” advisor.

Qbd By Pharmaceuticals

Even though the pharmaceutical industry has focus on quality, it has failed to keep up with other industries in terms of manufacturing efficiency and productivity.

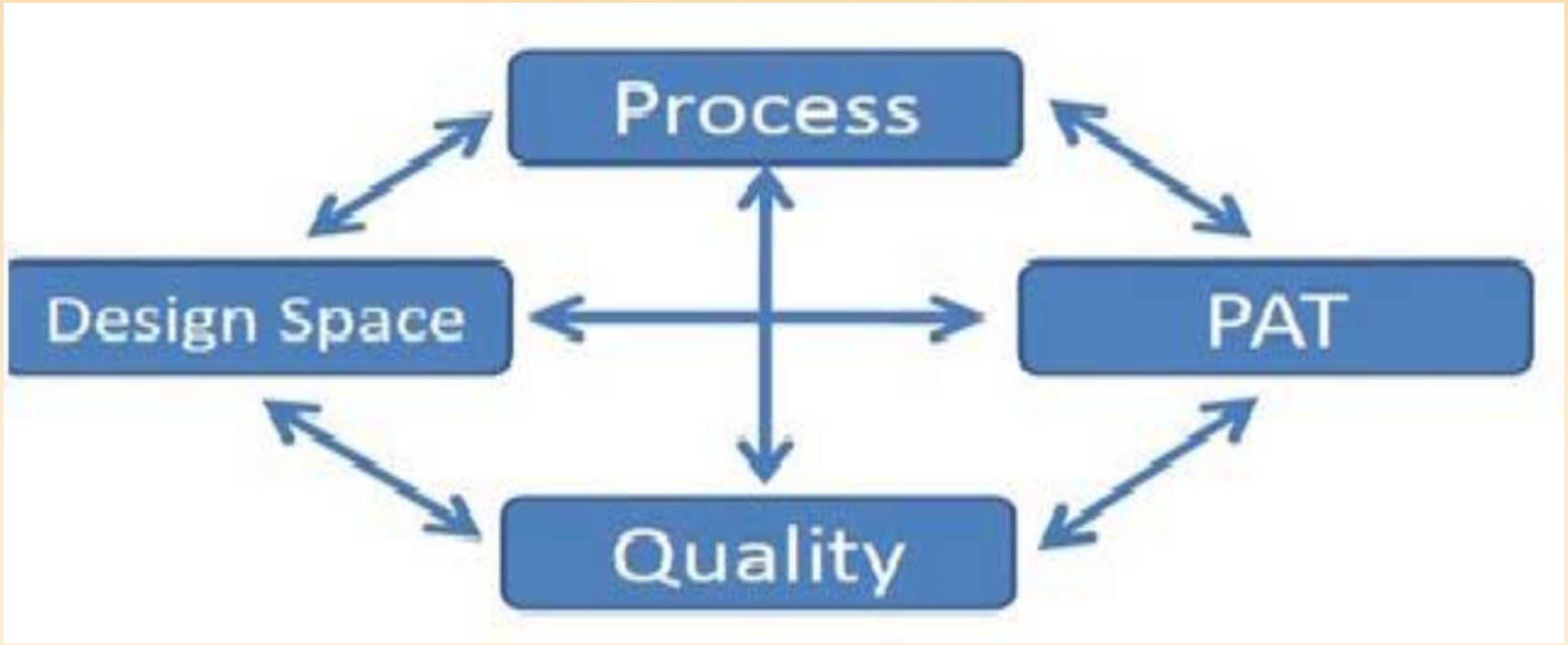
Current scenario in the Pharmaceutical Industry:

- Cost of revalidation
- Off-line analysis for in-process - need based
- Product specifications as primary means of control
- Unpredictable Scale-up issues
- Inability to understand failures

Systematic approach to development:

- That begins with predefined objectives
- Emphasizes products and process understanding
- Process control

Process, Quality, Design and PAT



Quality Target Product Profile

A summary of the drug development program described in terms of labelling concepts and it mainly focus on the safety and efficacy.

- Description
- Clinical Pharmacology
- Indications and Usage
- Contraindications
- Warnings
- Precautions
- Adverse Reactions
- Drug Abuse and Dependence
- Over dosage
- Dosage and Administration
- How Supplied
- Animal Pharmacology and/or Animal Toxicology
- Clinical Studies

Formulation Design and Development

Not all prototype formulations can be evaluated in human subjects, which mean that developing sensitive in vitro dissolution methods is crucial to an effective development program.

Manufacturing Process Design And Development

- Process development and formulation design cannot be separated because a formulation cannot become a product without a prescribed process.
- Process design is the initial stage of process development, in which an outline of the commercial manufacturing processes is documented, including the intended scales of manufacturing.

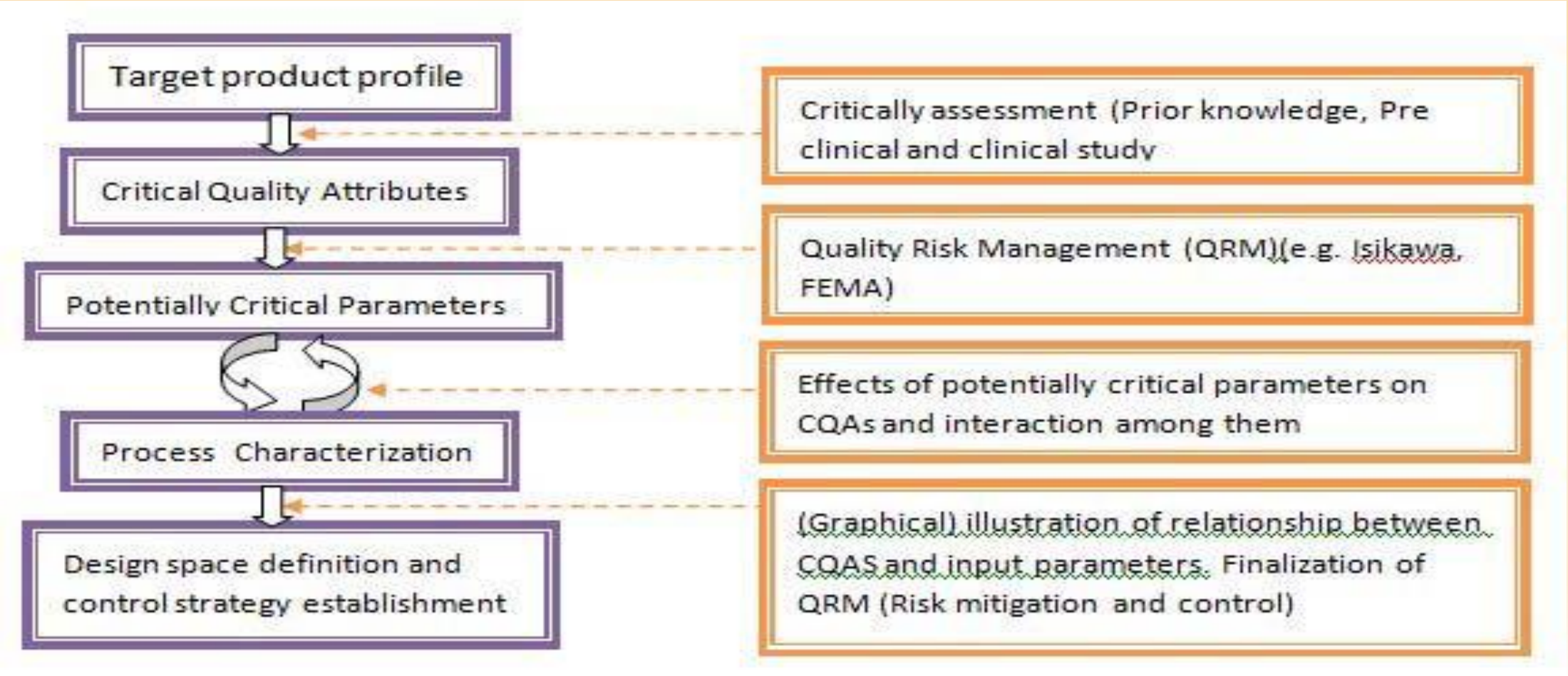
Manufacturing Process Design And Development

- The outline should include all the factors that need to be considered for the design of the process, including facility, equipment, material transfer, and manufacturing variables. Other factors to consider during process development are the QTPP and CQAs.

Product quality by end product testing Vs QbD

- Comparison is shown between product qualities by end product testing vs. quality by design
- Flow-chart for Product Quality by End Product Testing

Simplified flow-chart of QBD process



Successful Adoption

- Regulatory flexibility to accommodate quality by design submissions
- Common dossier accepted worldwide by regulatory agencies
- Post-approval changes within pre-defined design space can be implemented with regulatory flexibility
- Laws and processes in place to protect intellectual property (IP)

Designed To Consistently Meet Desired Product Quality

- Design space concept
- Experimentally defined process operating space based
- on scientific principles. Critical process parameters identified.
- Critical - impact product quality.
- Space - operating range yielding acceptable product Space.
- Critical process parameters are consistently controlled.
- Product of process is always desired quality Product.
- End product testing might be reduced.

Designed to facilitate continuous improvement

- Process control strategy: control of the process.
- Performance and continuous process improvement.
- Real-time process feedback Process improvements within design space Knowledge builds with experience Leverage information/new technologies to improve process efficiency Key opportunity to continuously improve the process. E.g. increased supply, more efficiency.

ICH Q8, Q9, Q10 GUIDELINES: THE FOUNDATION OF QbD

ICH Guidelines Q8 for Pharmaceutical Development, Q9 for Quality Risk Management, Q10 for Quality systems are foundation of QbD

Quality by Design relative to ICH

- Concepts aligned
- Design Space - Key to understanding
- Process robustness
- Design of Experiments (DOE)
- Quality management Quality management

Design Space

- Multidimensional combination with interactions Multidimensional interactions put variables (e.g. raw material attributes) and process parameters
- Demonstrated to provide assurance of quality
- Defined by applicant and reviewed by regulator Defined regulator
- Once design space is approved, regulatory post approval change requirements will be simplified approval Inside vs. outside design space Inside space
- Regulatory flexibility to operate within the design space Regulatory space

Development of Design Space: Science based Product and Process Design in Development

- Enhance process understanding to support science based approach
- Integration of drug substance and drug product process development at the interface.
- Drug substance properties designed for downstream manufacturing process

Utilization of Design Space: Effective Process Control and Quality System

- Use of extensive monitoring during development to enhance process understanding.
- Use science based control during manufacturing.
- However, process control may be limited by time needed for biological assays.

Applications Of Quality By Design

- Quality by design (QbD) – a comprehensive systematic approach to pharmaceutical development and manufacturing.
- Advancement in the pharmaceutical development and manufacturing by Qbd can be explained against traditional approach.

Aspects	Traditional	QbD
Pharmaceutical Development	Empirical	Systematic; Multivariate experiments
Manufacturing Process	Fixed	Adjustable within design space; opportunities for innovation
Process Control	In process testing for go/on-go; offline analysis wide or slow response	PAT utilized for feedback and feed forward at real time
Product Specification	Primary means of quality control; based on batch data	Part of the overall control strategy, based on the desired product performance
Control Strategy	Mainly by intermediate product and end product testing	Risk based; controlled shifted up stream, real time release
Lifecycle Management	Reactive time problem and OOS; Post approval changes needed	Continual improvement enabled within design space

Qbd For Drug Products

- A natural extension of Target Product Profile for product quality – Quality characteristics (attributes) that the drug product should possess in order to reproducibly deliver the therapeutic benefit promised in the label guide to establish formulation strategy and keep the formulation effort focused and efficient ..
- It facilitates identification of what's needed/critical for the patient/consumer in the Quality Target Product Profile(such as Critical Quality Attributes, CQAs)
- A drug product designed, developed and manufactured according to Quality Target Product Profile with specification (such as dissolution/release acceptance criteria) consistent with the desired in vivo performance of the product.

Critical Quality Attributes

- It is necessary to identify the quality attributes that are critical, i.e. those defining purity, potency and surrogate for Bioavailability Criticality etc. It is based on the impact of quality attribute/ parameter on the safety, efficacy & quality (manufacturability) of the product.
- Establish a link between CPP & CQAs: Identification of attribute or parameters that can be used as surrogate for clinical safety & efficacy (important to patient) .
- Manufacturability is also an attribute (important to business) that is critical to quality.
- The level of criticality may differ for an API manufacturing process relative to a drug product manufacturing process.

- API is one component of a drug product and one step further away from the patient continuum of Criticality.
- Several levels of criticality may be used to describe multiple levels of risk. As attribute or parameter boundaries approach edges of failure, the level of critically increased with the risk.

The Target Product Quality Profile (TPQP)

Target Product Quality Profile (TPQP) is a tool for setting the strategic foundation for drug development —“planning with the end in mind.” More recently an expanded use of the TPP in development planning, clinical and commercial decision making, regulatory agency interactions, and risk management has started to evolve.

Office of New Drug Quality Assessment (ONDQA)

- Science-based assessment
- Restructured organization and reorganized staff –premarket staff and post market
- CMC Pilot
- A number of applications submitted
- Lessons learned
- Evaluation of information
- Implementation of PMP

Office of Generic Drugs (OGD)

- QbD contains the important scientific and regulatory review questions
- Evaluate whether a product is of high quality
- Determine the level of risk associated with the manufacture and design of this product.

- 416 applications received using QbD by June 2007
- Successful in ensuring that questions address issues regarding QbD

Office of Biotechnology Products

- Have more complex products
- Already doing some aspects of QbD
- In process of preparing to accept applications using QbD
- Beginning a pilot for biotech products for QbD –using mainly comparability protocols
- mainly comparability protocols Also implementing Q8, Q9 and Q10

Drug Substance

Drug substance means “an active ingredient that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure or any function of the human body, but does not include intermediates use in the synthesis of such ingredient.”

Drug Excipient

“The word excipient is derived from the Latin **excipere**, meaning ‘to except’, which is simply explained as ‘**other than**‘. Pharmaceutical excipients are basically everything other than the active pharmaceutical ingredient. Ideally, excipients should be inert, however, recent reports of adverse reactions have suggested otherwise.”

Drug Substance and Excipient Properties

To consistently achieve the drug-product quality specified in the label, the drug substance needs to be thoroughly characterized with respect to its physical, chemical, biological, and mechanical properties such as solubility, polymorphism, stability, particle size, and flow properties.

Process Analytical Technology (PAT)

“A system for designing and controlling manufacturing through timely measurements (i.e. during processing) of critical quality and performance attributes for raw and in process materials and also processes with the goal of ensuring final product quality into the product and manufacturing processes, as well as continuous process improvement.

Process analytical technology (PAT) has been defined by the United States Food and Drug Administration (FDA) “as a mechanism to design, analyse, and control pharmaceutical manufacturing processes through the measurement of Critical Process Parameters (CPP) which affect Critical Quality Attributes (CQA)”.

PAT is a system and application at following sites

1. Designing, analysing and controlling manufacturing.
2. Timely measurements.
3. Critical quality and performance attribute.
4. Raw and in-process materials.
5. And processes.
6. RM Testing (warehouse based)
7. Packaging Components
8. Blending (at- line or on- line)
9. Drying
10. Tableting (potency and CU)
11. Encapsulation (Coating thickness)
12. Packaged product
13. Equipment cleaning
14. Equipment cleaning (surface monitoring)

The objective for PAT implementation could be one or more of the following

- Better process understanding
- Improved yield because of prevention of the scrap, rejects, and reprocessing
- Real-time release of the batches From an implementation perspective, perhaps, PAT can be visualized as the three-step process [19, 20]. The design phase starts early in process development when the given unit operation is being designed and then later optimized and characterized [21,22]. In this phase, the critical quality attributes (CQA) that are being affected by the process step are identified along with the critical process parameters (CPP) that have been determined to affect the CQA. This process understanding is the essence of PAT and critical for the next two phases. Discuss the need for general FDA guidance to facilitate the implementation of the PAT.

- Decrease in the energy consumption and improved efficiency from conversion of the batch process into a continuous process
- Cost reduction because of reduced waste and reduced energy consumption
- Reduction in the production cycle time by using online/at-line or in-line measurements and control

PAT Goals

- Approaches recognize Product quality and performance are ensured through the design of effective and efficient manufacturing processes.
- v Product and process specification are based on a mechanistic understanding of how formulation and process factors affect product performance.
- v Continuous “real time” quality assurance.
- v Relevant regulatory policies and procedures are tailored to accommodate most current level of scientific knowledge.
- v Risk-based regulatory,

When implementing QbD and PAT Framework Technologies a life sciences company should consider the following kinds of QbD and PAT developmental requirements:-

- Development of process modelling capabilities that allows for real-time monitoring, feedback and control versus statistical packages that only provide data after the fact
- Consider applicable modelling and optimized processes from other industries
- Provide an end-to-end solution…from PAT to modelling to visualization to optimization and ultimately to automated release capabilities
- Develop and maintain a library of strong process models. This allows for fewer deviations, higher quality product, less waste or rejects and provides a shorter time to product release
- Create a PAT framework that provides an integrated harmony with Quality by Design, legacy/new equipment, data analysis, process control and regulatory compliance.

Four key elements in PAT implementation:

- **Building a science:-**based knowledge base complete process understanding at the mechanistic and first principle level

- **Process monitoring and control:** determination of critical process parameters and critical quality attributes and selection of measurement, analysis and control mechanisms to adjust the process to provide the predicted quality of the product.

- **Validation of PAT system.**
- **Regulatory strategies.**

Building a science – based knowledge base:

- The PAT guidance emphasizes the need to develop a deep understanding of the underlying scientific principles behind pharmaceuticals manufacturing processes to determine the parameters critical to process and product quality. The knowledge base provided by the PAT approach is valuable in three main ways:

    a) It is a foundation for robust process and product design.

    b) It facilitates continuous learning throughout the product life cycle.

    c) It is supports and justifies flexible regulatory paths for innovative new approaches.

- The design of experiments, and the capture and evaluation of analytical measurement data are essential parts of building the knowledge base.

Examples of sources of variation

- Variation in the raw material supplier manufacturing processes that impact the chemical and physical attributes of the supplied materials.
- Time based variation in manufacturing performance (e.g., between equipment maintenance events).
- Effects linked to planned changes to equipment / analyser hardware and software of the system.
- Individual ways of working (i.e., variation attributable to people in manufacturing area).
- Change in the local environment (e.g. temperature, humidity and other environmental condition).
- Long term equipment ageing and degradation effects.

Process monitoring and control

- The understanding of the interaction between process and product is the basis for the design of the process monitoring, process control and QA strategies used in Manufacturing PAT is an integrated approach in which the results obtained from the real time analysis of critical process control points are used to control the process in some way. During manufacturing, process parameters are adjusted (within clearly defined limits) to produce the desired product quality attributes at the process end point. The automation system required for this level of process control are available today and are used extensively in the chemical and petrochemical industries.

Technologies used in PAT include

- Near infra red (NIR), Raman spectroscopy, UV – visible Spectrophotometry, Fourier Transform Infrared (FTIR), X-ray Powder Diffraction (XRPD), Terahertz Pulse (TP) spectroscopy, NIR microscopy, Acoustic Resonance (AR) spectrometry, thermal effusivity, etc. NIR spectroscopy is the most popular and widely used technique.

Validation of PAT system

- The validation plan for a PAT system will typically include the validation of Software packages for data analysis Process analyser hardware and software Process control software IT systems for the management, storage and backup of Results

Regulatory strategies

- A PAT policy development team of four subject matter experts has been established to work with industry to facilitate discussion on proposed pat approaches at an early stage and support FDA’s sciences and risk based approaches to PAT. PAT is a joint initiative of the centre for Drug Evaluation and Research (CDER), Office of Regulatory Affairs (ORA) and the Centre for Veterinary Medicine (CVM) within the “cGMPs for the 21st Century "framework.

PAT applications in the pharmaceutical industry

Application	Process analyzer	Statistical tool	Observation
Rapid and accurate tablet identification	Acoustic resonance spectroscopy	Principle-components analysis (PCA)	A fast and non-destructive method for on-line analysis and label comparison before shipping, to avoid mislabeling of drug [23]
Active determination of content of uncoated pharmaceutical pellets	NIR	Partial least-squares (PLS) analysis	NIR method was developed and validated for determination of active content ranging from 80-120% of the usual active content of the uncoated pharmaceutical pellets [24]
Mechanical property determination of the drug tablet	Air-coupled excitation and laser interferometric detection	Iterative computational technique	Examination of the vibrational resonance frequencies can be directly correlated with the mechanical properties of the tablet providing a non- destructive technique for physical characterization of the tablet [25]
Analysis of sustained-release tablet film coatings using terahertz pulsed imaging (TPI)	Terahertz pulsed spectroscopy (TPS)	-	Tablet coating thickness, coating reproducibility, distribution, and uniformity can be easily determined. The method was validated against optical microscopy imaging [26]
Roller compaction process of dry Granulation	Thermal effectivity measurement using the effectivity sensor	-	Effectivity measurement were used to monitor the roller compaction process [27]

Quality Assurance & Quality Control QbD

Why Quality is important in pharmaceuticals?

- The pharmaceutical environment today is changing quickly due to globalization, increased competition, cost constraints, demands for efficiency, development of international regulation, supply chain complexity, and product/process complexity. In this fast-changing environment, the people and companies that learn to adapt will prosper.
- To manufacture & deliver consistently zero-defect products to the patients.
- The quality, efficacy and safety attributes of products must be ensured so that the consumer health is not compromised.

Impacts of ignorance on Quality

- Manufacturing process
- Packaging
- Transportation
- Storage condition

- Lack of therapeutic effect:
  - Prolonged illness
  - Death
- Toxic and adverse reaction
- Waste of limited financial resources
- Loss of credibility

QUALITY

A measure of excellence or a state of being free from defects, deficiencies and significant variations.

QUALITY ASSURANCE

Obtaining confidence that, required quality of product or service is satisfactory for their intended use.

QUALITY CONTROL

Part of GMP concerned with sampling, testing and specifications

Functions of QA in Pharmaceutical industry

- Raw materials used in the manufacturing are approved and procured from approved vendor.
- All data's are recorded as per cGMPs and is reviewed for accuracy and traceability.
- Procedures are in place for performing the activities, operating and calibrating the equipment
- Quality is built up in the plant, process, product. That a Robust Quality system is in place
- Trainings like induction, On job, Scheduled and after any changes are conducted to respective individuals on time.

To prepare and approve Quality Policy, Quality Objectives, Quality Manual and Validation Master Plan.

- Periodic Monitoring of the Quality Objectives.
- Monitors all validation & stability activities are completed as per the schedule.
- Ensures that all changes impacting the product and the established systems are documented and reviewed to analyse the impact.
- Ensures that all deviations, OOS/OOT & Market complaints are logged, investigated to identify the root cause so as to take CAPA to prevent recurrence.
- Preparation of Annual product quality reports, trending of data, determining product and process performance.
- To arrange and conduct the self inspection, identify gaps and take CAPA. Review of related batch manufacturing records and QC testing data Prior to release of any batch.

Quality Control

Performs following activities

Routine

- RM &PM analysis
- Intermediate stage analysis
- Finished Products analysis
- Stability Studies

Non Routine

- Calibration & Preventive maintenance of instruments
- Preparation of reference/working standards

Activities managed through

- Instrumental Analysis
- Chemical Analysis (RM & FG)
- Microbiological Analysis
- Packaging Material Analysis

Functions of QC in pharmaceutical industry

Preparation of specifications for testing of materials and products.

- Carrying out Sampling and testing of materials or products.
- Environment Monitoring
- Conducting stability studies.
- Investigating test failures such as OOS / OOT / OOAC / OOAL.
- Analytical method validation.
- Evaluation of complaint samples.
- All the quality control activities are performed adherence to the GLP.

Quality Metrics

- A tool (ISPE: International Standards for Pharmaceutical Engineers) for continuous improvement in Quality
- It is a measurement standard by which efficiency, performance, progress compliance or quality of a process, or product can be assessed.

1)KPI’s shall be identified based on impact on organization goals and quality.

2. Weightage to be provided for each KPI.

3. Scoring to be provided for each KPI based on actual performance.

4. Communication to top management.

5. Necessary developments to be made to improve the failed KPI

Standard and regulatory requirements

1.Regulatory aspects to QbD

- FDA perspective
- ICH guideline and QbD
- Regulatory challenges and inspection

2.Basic considerations of QbD

Elements of pharmaceutical development

- Define an objective
- Determination of critical quality attributes.(CQA)
- Risk assessment
- Development of experimental design
- Designing and implementing control strategy
- Continuous improvement throughout product life cycle

3.Application of QbD in analytical methods of measurement

- Aspects of application of QbD to analytical method,
  - Analytical target profile (ATP)
  - Method design
  - Critical quality attributes (CQA)
  - Risk assessment
  - Method qualification
  - Control strategy
  - Life cycle approach

4.Literature reports of application QbD or elements of QbD to analytical method

- For chromatographic technique
  - In determination of impurity
  - In screening of column used for chromatography
  - In development of HPLC method for drug products/substances
  - In capillary electrophoresis
  - In stability studies
  - In UHPLC

5.For hyphenated technique

- In LC–MS method development
- In bio analytical method development
- In dissolution studies
- For spectroscopic measurements
  - i) In handling complex spectroscopic data
  - ii) In mass spectroscopy
  - iii) In near infrared.

6.Other applications of QbD or elements of QbD

- Pharmaceuticals
- In sterile manufacturing
- In solid oral dosage form
- Contribution of (SEM/EDX) to QbD by investigation of pharmaceutical materials
- In gel manufacturing
- QbD for ANDAs
- In tableting process
- Impact of genotoxic impurities on process development
- In co-precipitation process
- Nanosuspension preparation
- In analysis of excipients and API

7.Biopharmaceuticals

- In manufacturing of protein
- In production and characterization of monoclonal antibody
- For chromatographic technique used for purification
- PAT and QbD for biopharmaceutical
- In Nano medicine
- Challenges and solution for application of QbD to
- Biopharmaceutical

8.Clinical

9.Genetics

10.Problems in adoption of QbD

Conclusion:

- The goals of implementing pharmaceutical QBD are to reduce product variability and defects , thereby enhancing product development and manufacturing efficiencies and post approval change management.

REFERENCES:

- 1.ICH guideline Q 8 –pharmaceutical development, http://www.ich.org
- 2.u.s .FOOD and DRUG administration for industry. PAT – a framework for innovative
- 3. Review article of quality by design (QBD)

ASEPTIC PROCESS TECHNOLOGY

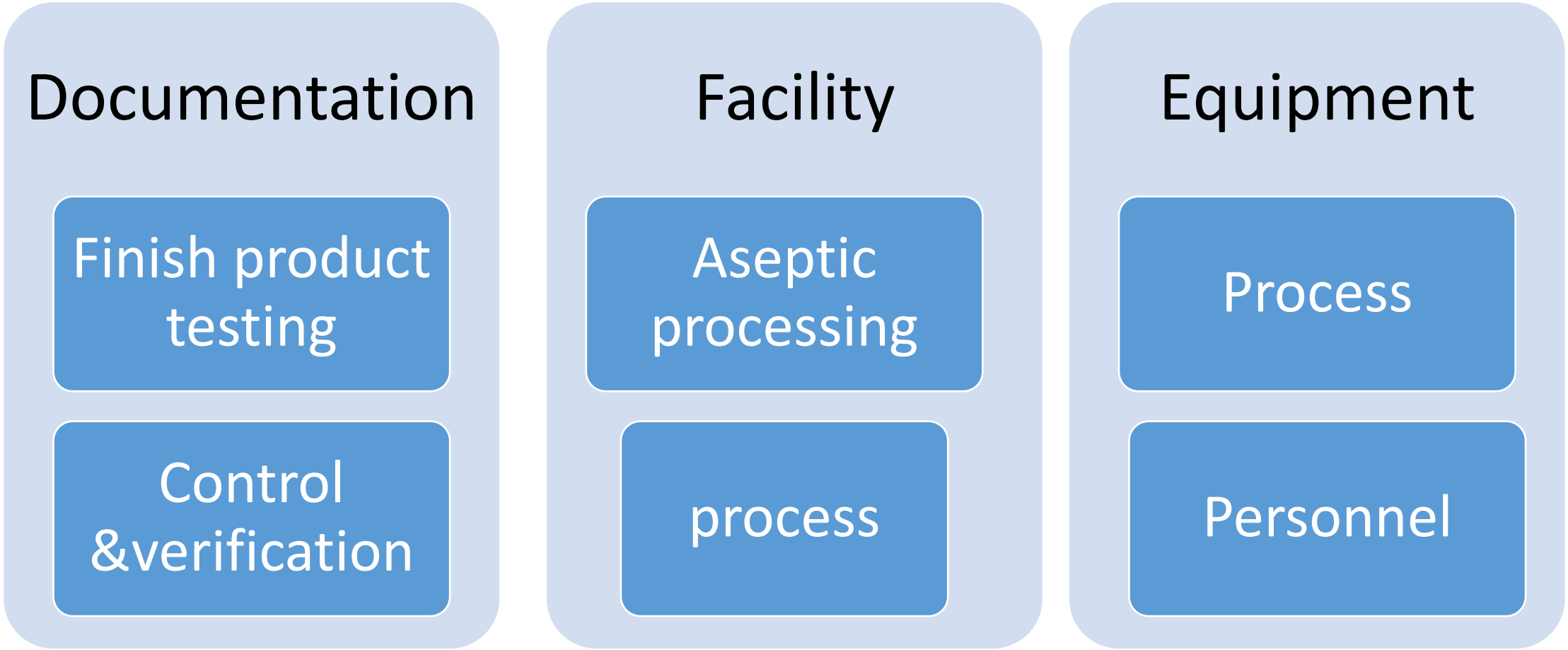
Introduction

- The production of sterile materials is divided into two major categories terminally sterilized using one or the other of the method described earlier in this chapter , or aseptic processing , in which individually sterilized item are assembled in a pristine environment into the final product.

- Interventions are to be avoided at all times in aseptic processing.
- Interventions always mean increased risk to the patient.

What is aseptic processing?

- ✓The production of sterile drug products by bringing together the product, container and closure that have been subjected to different sterilization methods separately, and assembled them in an extremely high quality environment by skilled personnel using the right tools.


Documentation
Finish product testing
Control &verification
Facility
Aseptic processing
process
Equipment
Process
Personnel

Content:

A) Introduction to Parentral suspension.

a) Formulation consideration.

b) Formulation development.

c) Evaluation of suspension.

B) Introduction to Parentral emulsion.

a) Formulation development.

b) Stability of emulsion.

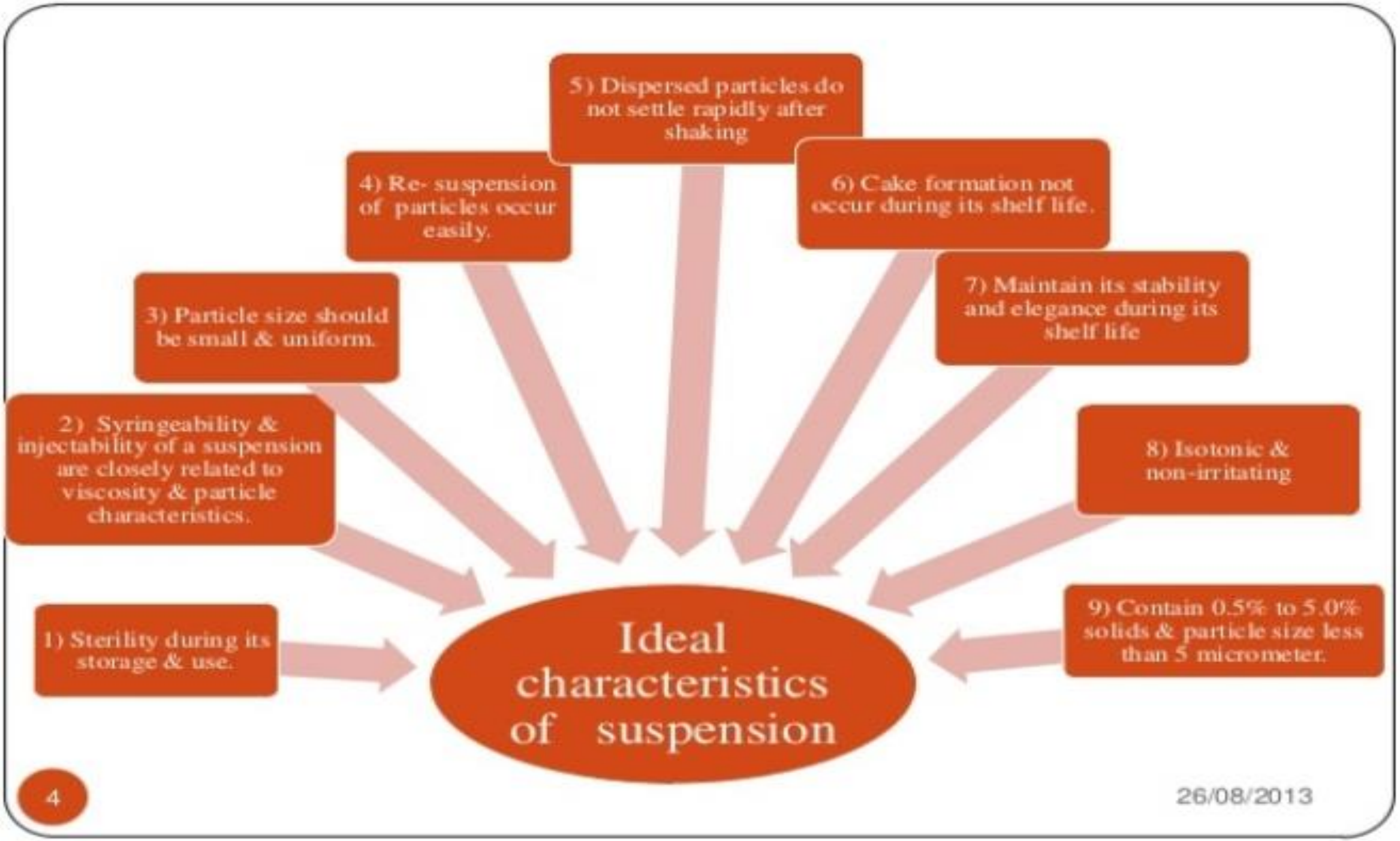
c) Evaluation of emulsion.

C) Packaging.

D) References.

Parentral Suspension:-

- **Introduction:** Parentral suspensions are dispersed, heterogeneous systems containing insoluble drug particles which, when are to be resuspended in either aqueous or oil vehicles before administering to a patient.
- They administered by either subcutaneous (S.C.) or intramuscular (I.M.) route.
- For example procaine Penicillin G.


5) Dispersed particles do not settle rapidly after shaking
4) Re- suspension of particles occur easily.
6) Cake formation not occur during its shelf life.
3) Particle size should be small & uniform.
7) Maintain its stability and elegance during its shelf life
2) Syringeability & injectability of a suspension are closely related to viscosity & particle characteristics.
8) Isotonic & non-irritating
1) Sterility during its storage & use.
Ideal characteristics of suspension
9) Contain 0.5% to 5.0% solids & particle size less than 5 micrometer.
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Advantages of parent ral suspension

1) Better for drugs that are insoluble in convention solvents.

2) Increased resistance to hydrolysis & oxidation as drug is present in the solid from.

3) Formulation of controlled released drug is possible

4) Elimination of hepatic first pass effect.

Disadvantages of parentral suspension

1) **Stabilization of suspensions for the period between manufacture & use present a number of problems**. e.g. solids gradually settle & may cake, causing difficulty in redispersion prior to use.

2) Maintenance of **physical stability** is very difficult in this dosage form.

3) **Non-uniformity** of dose at the time of administration.

4) **Difficulty in manufacturing**: Special facilities required to maintain aseptic condition for manufacturing processes such as : crystallization, particle size reduction, wetting, sterilization

5) **Difficulty in formulation**: selecting the ingredients, like suspending agent, viscosity inducing agent, wetting agent, stabilizers and preservative.

Formulation Considerations:

Factors affecting release of drug from suspension:

1) Solubility of drug in biological fluids at the injection site.
2) Lipid solubility and oil-water partition coefficient of the drug.
3) pKa of the drug.
4) Dissolution rate of solid from its dosage from.
5) Particle size of the of drug in suspension.
6) Compatibility with other ingredient.

Formulation Considerations:

Preformulation data needed for the formulation development:

I. Particle size and particle size distribution.

II. Dissolution.

III. pKa.

IV. Solvates and polymorphs.

V. Solubility.

VI. pH stability.

Formulation development:

- **Suspension ingredients:** Parentral suspension contain both active ingredient(s) and excipients.
- **Excipients used in the parentral preparations must be….**

➢ Physically and chemically compatible with active ingredient.

➢ Nonpyrogenic, nontoxic, nonhaemolytic and nonirritating.

➢ Must not interfere with the therapeutic effect of the active ingredient.

➢ Must maintain stability during sterilization and during the shelf life

➢ Effective at low concentration.

Typical excipients used in parentral suspensions:

1) **Flocculating/suspending agents:**
2) **Wetting agent**
3) **Solvents**
4) **Preservatives**
5) **Antioxidants.**
6) **Chelating agents.**
7) **Buffering agents.**
8) **Tonicity agents.**

1) Flocculating/suspending agents:

a) Surfactants: e.g. Lecithin, Polysorbate 20, Polysorbate 40, Polysorbate 80,Pluronic F-68.

b) Hydrophilic colloids: e.g. Sodium CMC, Acacia, Gelatin, MC, PVP.

c) Electrolytes: e.g. Potassium/sodium chloride, Potassium/sodium citrate, Potassium/sodium acetate.

2) Wetting agent: They reduce the contact angle between the surface of the particle and the wetting liquid.

- Useful when hydrophobic powders are suspended in aqueous systems.

e.g. Nonaqueous solvents (glycerin, alcohol, and propylene glycol).

Non ionic surfactant. (polysorbate 80, Polysorbate 20,Polysorbate 40).

3) Solvents: May be aqueous or non aqueous.

Water for injection is preferred aq. solvent system.

- Non aqueous solvent may be..

i. Water miscible (Ethanol, Glycerin, Propylene glycol, N-(β hydroxyethyl)-lactamide.

ii. Water immiscible includes fixed oils like Sesame oil, Peanut oil, Castor oil, almond oil, sunflower oil, iodinated poppy seed oil.

4) Preservatives:

- Benzyl alcohol (0.9% to 1.5%), Methylparaben (0.18% to 0.2%), Propylparaben (0.02%), Benzalkonium chloride (0.01 % to 0.02%), and Thimersal (0.001 % to 0.01 %).

5) Antioxidants:

a) **water soluble:** Ascorbic acid- 0.02-0.1%, Sodium bisulfite- 0.1-0.15%, Sodium metabisulfite- 0.1-0.15 %, Sodium formaldehyde sulfoxylate- 0.1-0.15%, Thiourea- 0.005%

b) **Oil soluble:** Ascorbic acid esters-0.01-0.15, BHT-0.005-0.02%, Tochopherol- 0.05-0.075%.

6) Chelating agents: EDTA

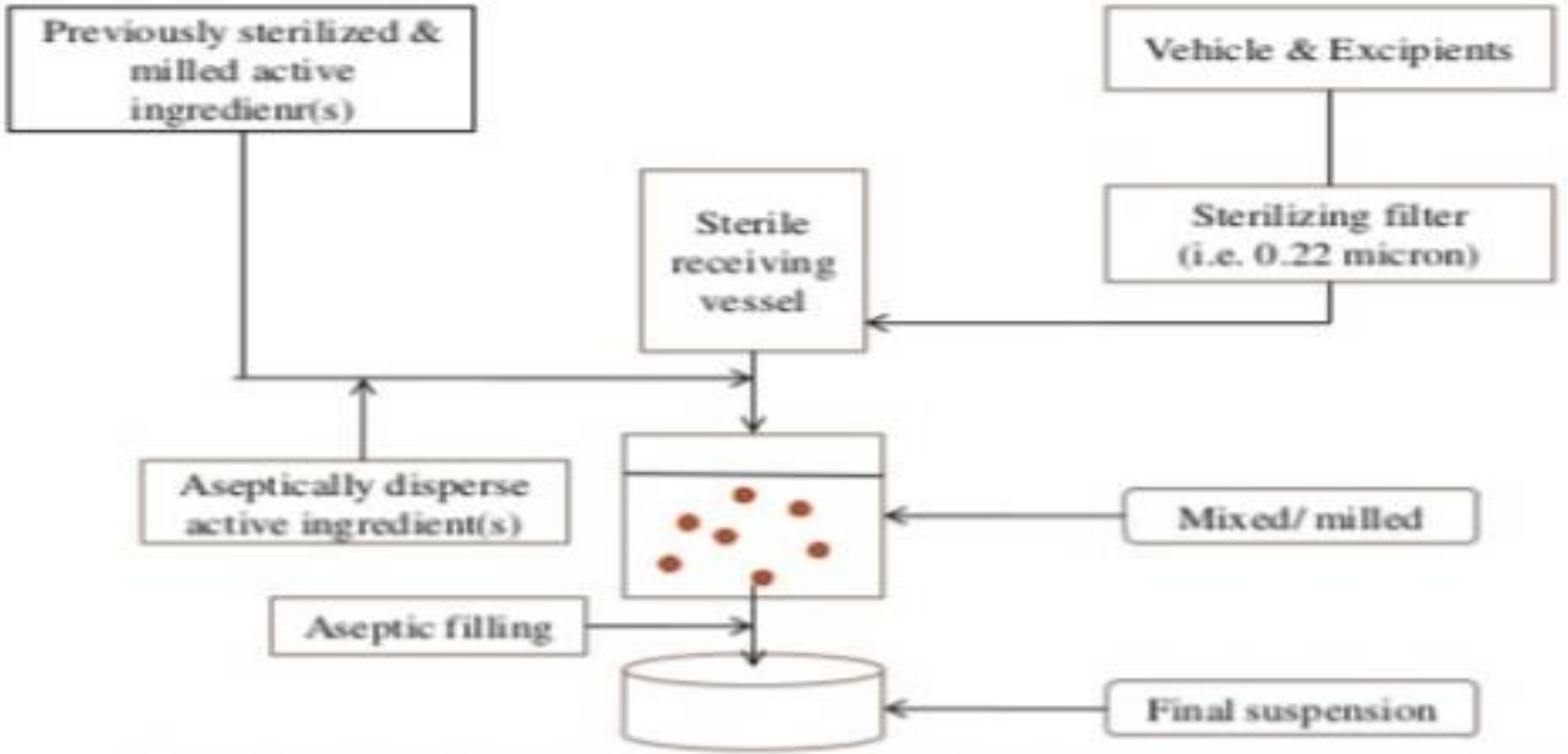
7) Buffering agents: Citric acid, Sodium citrate.

8) Tonicity agents: Dextrose, Sod. Chloride.

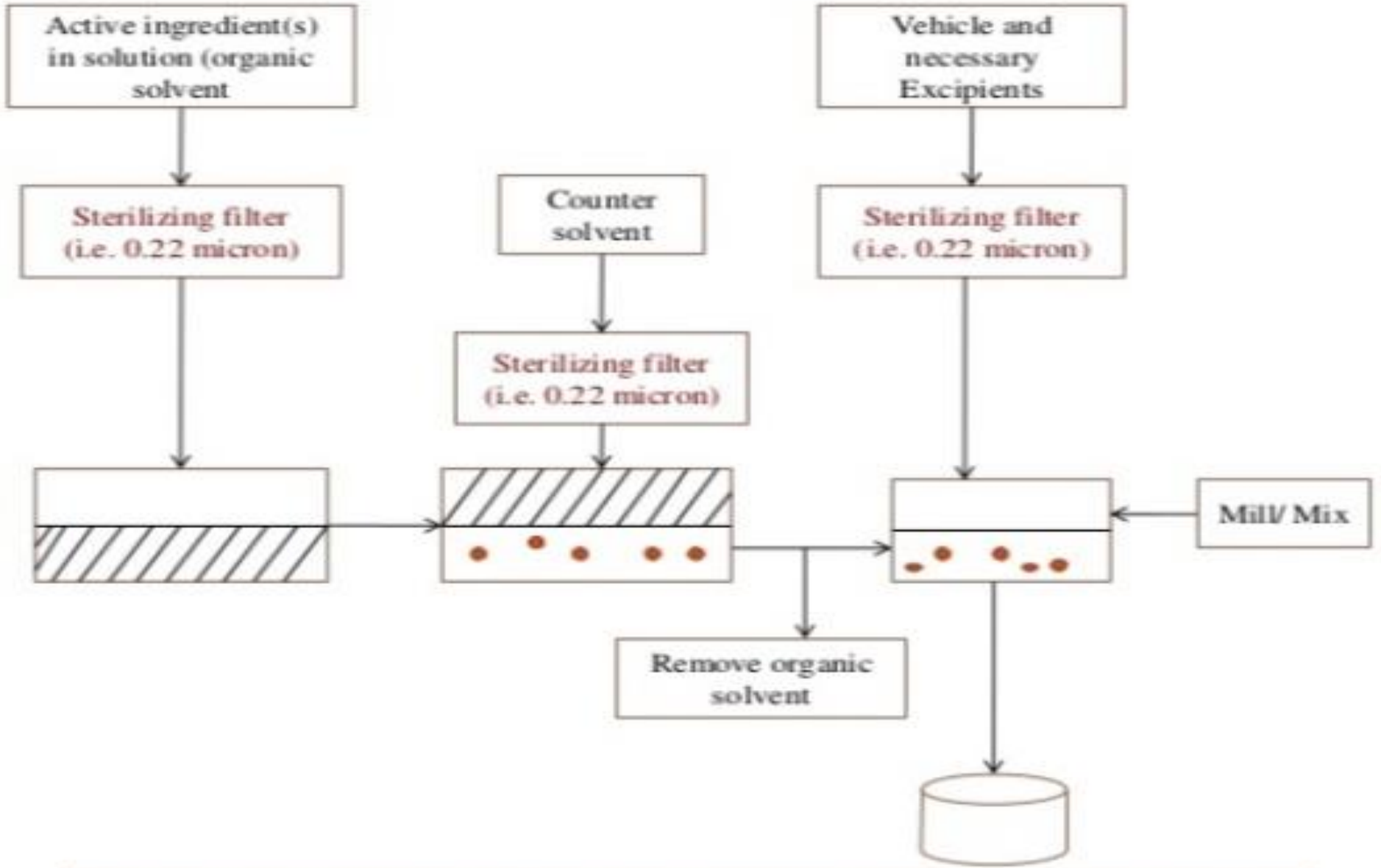
Manufacturing Considerations:

- Two basic method used to prepare Parentral suspension are-

1. Aseptically combining sterile powder and vehicle
2. In situ crystal formation by combining sterile solutions.



1. Aseptically combining sterile powder and vehicle



2. In situ crystal formation by combining sterile solutions.

Stability and Evaluation:

A. Physical:

a) Syringeability.
b) Injectability
c) Resuspendibility.
d) Sedimentation Volume.
e) Freeze-Thaw cycles.
f) Crystal Growth.
g) Particle Size Measurement.
h) Zeta Potential determination.
i) Shipping Characteristic.
j) Product-Package Interaction.

B) Biological:

a) Sterility test.

b) Pyrogen test.

Official example of parentral suspension:

(1) Sterile ampicillin suspension USP'95 dispense as powder which is to be reconstituted at time of administration.

(3) Tetanus toxoid adsorbed USP'95, IP'96 – aq. Suspension.

(4) Betamethasone acetate suspension USP'96 aq. Suspension.

(5) Insulin Zinc suspension USP'95, IP'96 aq. Suspension.

(6) Procaine penicillin suspension IP'96

- **Parentral Emulsion:**
- **Introduction:** Parentral emulsion is O/W or W/O emulsion with mean droplet diameter 200-500 nm.
- Mainly employed as Total parentral nutrition's.
- These are milky white in appearance.
  - W/O emulsion (S.C.).
  - O/W Sustained release depot preparation (I.M.).
  - O/W nutrient emulsion (I.V.)

Emulsion Ingredients:

A) Oils : The oils most commonly used are Long Chain Triglycerides (LCTs) from vegetable sources (soybean or sunflower oil.)

B) Emulsifiers: Natural and synthetic emulsifier are

a) Natural emulsifier- eg. lecithins.

b) Synthetic emulsifier- eg. Spans and Tweens.

C) Aqueous phase: a) Water for injection is aqueous phase for parentral emulsion.

b) Various substances have been added to the aqueous phase to adjust osmolarity, pH.

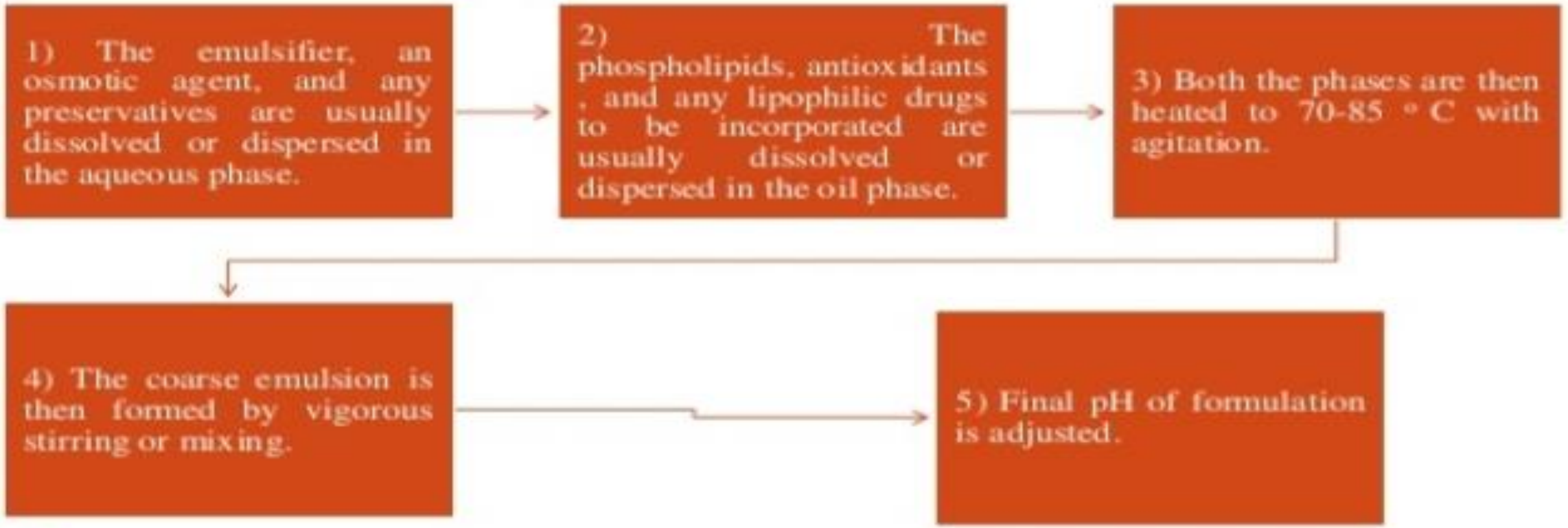
D) Tonicity modifier :- Glycerol, sorbitol, xylitol are added in aqueous phase.

E) Antioxidants :- α-tocopherol, ascorbic acid may be added in aq. Phase to prevent peroxidation of unsaturated fatty acids.

F) Preservatives :- p-hydroxy benzoic acid (methyl and butyl derivatives) can be dissolved in the aqueous phase.

Emulsion Manufacture:

A) Formulation Preparation:



B) Homogenization and particle size reduction: Can be done by

a) Ultrasonic homogenizers,

C) Filtration: Membrane filter is used for final filtration to remove larger particles.

D) Sterilization: For large-volume (l00 to 1000 ml.) injectable fat emulsions, sterilization is achieved by autoclaving.

Stability of parentral emulsions:

1) Stability of the formulation: Influenced by processing conditions, autoclaving, storage conditions, excessive shaking, or the addition of electrolytes or drugs.

2) Physical stability: Indicated by

a) Particle size changes.

b) Flocculation.

c) Creaming, coalescence.

d) Extreme temperature fluctuation such as freezing can result in an increased oil droplet size, leading to aggregation, coalescence, and ultimate separation.

3) Chemical Stability: Indicated by

a) Oxidation.

b) Hydrolysis.

c) Change in pH.

d) Rancidity of oil.

4) Microbiological Stability: For bacterial and fungal growth.

- Precaution should be taken to prevent microbial contamination during processing and maintain sterility.

Evaluation of Emulsions:

1) **Physical examination:** Visual observation of creaming, coalescence, and oil separation.

2) **Chemical analysis:** Determination and characterization of drug substance, oil, phosphatide, and excipients present, including free fatty acids and oxidative degradation products.

3) **pH determination.**

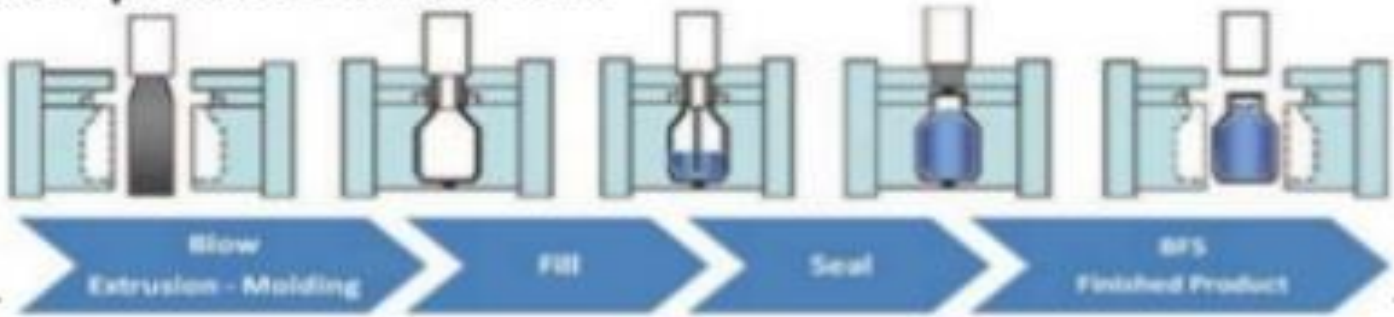
4) **Particle size surface charges.**

5) **Sterility test.**

6) **Pyrogen test.**

Packaging for parenteral Suspension and Emulsion:

- Container components for parenteral products must be considered an integral part of the product because they can dramatically affect product stability, potency, toxicity, and safety.
- Injectable suspension and emulsions provided in volumes of 100 to 1000 ml are packaged in USP type I & II Glass bottles.
- Siliconized Bottles with hydrophobic inner surface can be used.
- Rubber closures are most commonly used.
- Closures must not be permeable to oxygen or become softened by contact with the oil phase of emulsion.



Small volume parenterals (SVPs):

1) Ampoules
2) Glass vials sealed with rubber stoppers
3) Plastic ampoules (blow-fill-seal)
4) Pre-filled syringes
5) Needle-free injection

Ampoules

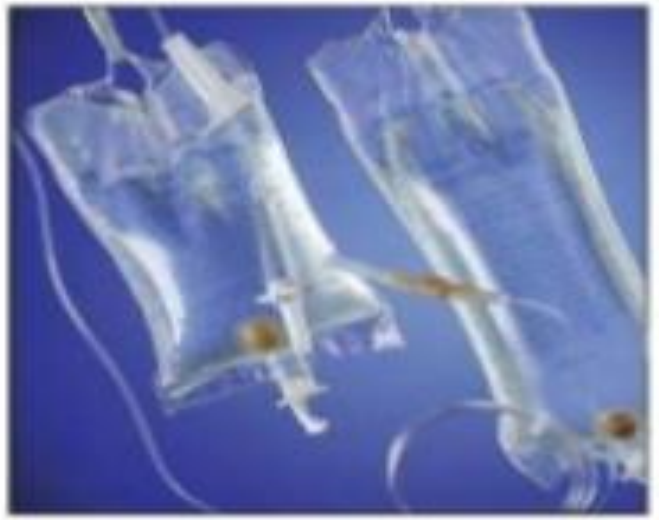
Glass vials

Plastic ampoules

Large volume parenterals (LVPs):

- Glass bottles sealed with rubber stoppers.
- Plastic bags.

Glass bottles



Plastic bags.

Emulsion	Drug	Company	Activity	Method	Status
Intralipid®a	Amb	SmithKline	antifungal	extemporenous	pre-clinical trials
Diazemuls®a	diazepam	Durnex, Denmark	sedation	de novo	marketed in Europe
Vitalipid®	vitamins	Kabi	nutrition	de novo	marketed in Europe
	PGE_1	GreenCross	vasodilator, inhibits platelet aggregation	de novo	marketed in Japan
Diprivan®a	Propofol	ICI, England	Anaesthetic	de novo	marketed in Europe

PROCESS AUTOMATION IN PHARMACEUTICAL INDUSTRY

S.GAYATHRI

MASTER OF PHARMACY

SMALL VOLUME PARENTERALS

- **Parenterals :**
  - Sterile pyrogen-free preparation intended for administration by injection under or through one or more layers of skin or mucous membranes.
  - **TYPES:**
  - 1.Small volume parenterals – volume ranges from 1 – 30 ml. may be given single dose or multiple dose.
  - 2.Large volume parenterals – volume range from 100 – 1000 ml. Mostly given as single dose.

- SMALL VOLUME PARENTERALS:
  - Usually range 1 – 30 ml in volume.
  - Mostly given as multiple doses.

  - DIFFERENT TYPES ARE:
    - Ampoules
    - Vials
    - Dry powders
    - Prefilled syringes

- AMPOULES:
  - Sealed glass containers with an elongated neck that must be broken off.
  - Most ampoules are weakened around the neck for easy breaking; these will have a coloured band around the neck.
  - A 5 micron filter needle should be used when drawing the contents of an ampoules into a syringe since glass particles may have fallen inside the ampoule when the top was snapped off.
  - In addition, it is useful to wrap an alcohol wipe or small piece of gauze around the top of the ampoules before breaking it. This will provide some protection to the fingers if the ampoule shatters and will also reduce the possibility of glass splinters becoming airborne.

- VIALS :
  - Drugs and other additives are packaged in vials either as liquids or lyophilized powders.
  - Made of glass plastic and are sealed with a rubber stopper.
  - A needle is used to add contents to or withdraw contents from the vial.
  - Before withdrawing contents from a vial, an equal volume of air is usually injected into the vial to pressurize the vial and aid in withdrawing the contents.
  - Vials may be designated for single-dose or multi-dose use.
  - Multi-dose vials contain a preservative to inhibit bacterial contamination once the vial has been used.

- DRY POWDERS:
  - Dry powder formulation are lyophilized or freeze-dried powders that must be reconstituted with some suitable solvent to make a liquid formulation before being withdrawn from the vial.
  - Some drugs are not stable in liquid form and so these drugs are put into the powder form and reconstituted just prior to use.
  - There are several solvents that might be used to reconstitute the dry powders; the most common solvents are sterile water for injection, Bacteriostatic water for injection, Sodium chloride injection etc.

- PREFILLED SYRINGES:
  - It consists of syringes which are prefilled with the drug solution.
  - There are two varieties of prefilled syringes. One type, a cartridge type package, is a single syringe and needle unit which is to be placed in a special holder before use.
  - Once the syringe and needle unit is used, they are discarded but the holder is used again with a new unit.
  - The other type of prefilled syringe consists of a glass tube closed at both ends with rubber stoppers. The prefilled tube is placed into a specially designed syringe that has a needle attached to it.
  - After using this type or prefilled syringe, all of the pieces are discarded.

- FORMULATION ASPECTS:
  - Water for injection (WFI)
  - Solutes
  - Added substances
  - Antimicrobial agents
  - Antioxidants
  - Pyrogens
  - Sterilization

- WATER FOR INJECTION (WFI) :
  - Sterile water for injection, USP is a sterile, non-pyrogenic preparation of water for injection which contains no bacteriostatic, antimicrobial agent or added buffer and is supplied only in single dose containers to dilute or dissolve drugs for injection.
  - According to USP, it contains 10 CFU/100 ml water.
  - For IV injection, add sufficient amount to a solute to make an approximately isotonic solution PH 5.0 to 7.0
  - No therapeutic activity and non – toxic.
  - Water purified by reverse osmosis and distillation.

- **SOLUTES :**

✓Added to give stability and efficacy to the preparation.

✓Eg. Sucrose, mannitol, lactose.

- **ADDED SUBSTANCES**:

✓All substance that can safeguard quality of preparation.

✓It may affect the solubility of the preparation, provide a preservation effect and enhance isotonicity.

- **ANTIMICROBIAL AGENTS** :

✓Eg. Phenol 0.5% w/v

✓ Chlorobutanol 0.5% w/v

- ANTIOXIDANTS :
- To presence products because of the ease with which many drugs get oxidized.
- Eg. Sodium bisulphite 0.1%
- BUFFERS :
- To stabilize pH.
- Eg. Citrates, acetates etc.

- **PYROGENS :**
- Metabolic products of microbial growth causing an increase in body temperature.
- Come from sources like solvent, medicament, apparatus and improper storage.
- It is very difficult to remove pyrogens because they are:

➢Thermostable

➢Water soluble

➢Unaffected by common bactericides.

- The bacterial substance lipopolysaccharide (LPS) in the cell wall of bacteria is an example of pyrogen.

- STERILIZATION :
  - Moist heat sterilization
  - Dry heat sterilization
  - Sterilization by filtration
  - Gas sterilization
  - Sterilization by ionizing radiation

- **MOIST HEAT STERILIZATION** :
  - Bacterial death by moist heat is due to denaturation and coagulation of essential protein molecules (enzymes) and cell constituents.
  - It can be used for a large number of injections, ophthalmic solution etc.
  - Methods used :
  - ➢ Autoclave
  - ➢ Tyndallisation
  - Autoclaving used to sterilize anything, which is not injured by steam and high temperature of sterilization. These include aqueous parenteral solutions e.g. distilled water, saline solution etc;.
  - Tyndallisation essentially consists of heating the substance to boiling point (or just a little below boiling point) and holding it there for 15 minutes, three days in succession. After each heating, the resting period will allow spores that have survived to germinate into bacterial cells; these cells will be killed by the next days heating.

- **DRY HEAT STERILIZATION** :
  - The killing of microorganisms by heat is a function of the time-temperature combination used. If the temperature is increased then the time required for killing all the bacteria will be decreased.
  - The vital constituents of cells such as proteins (enzymes) and nucleic acids are denatured by oxidation.
  - Cycles recommended as per BP 1988 are:
  - ➢A minimum of 180 C for not less than 30 minutes.
  - ➢A minimum of 170 C for not less than 1 hour.
  - ➢A minimum of 160 C for not less than 2 hour.
  - Dry heat is used to sterilize glass ware (e.g. test tubes, petri dishes. Flasks, glass syringes etc.)

- **STERILIZATION BY FILTRATION**:
- This method is used for sterilizing thermo-labile solutions, which will otherwise be degraded by other conventional heating methods.
- The drug solutions are passed through the sterile bacteria proof filter unit and subsequently transferring the product aseptically into the sterile containers which are then sealed.
- Different types are:

➢Sintered glass filter

➢Seitz filter

➢Ceramic filter

- They are suitable for sterilizing aqueous and oily solutions but not for organic solvents such as alcohol, chloroform etc.

- **GAS STERILIZATION:**
- This process involves exposure of materials to sterilizing gases such as ethylene oxide, formaldehyde, glutaraldehyde, propylene oxide.
- Ethylene oxide is the only gas that is successfully used on a large scale of industrial and medical applications.
- It works by alkylation.

- **RADIATION STERILIZATION:**
- Different types of radiation used for sterilization are
  - Ultraviolent radiation
  - Gamma radiation
  - Infrared radiation
  - X- rays
  - Alpha and beta radiation
- Only a narrow range of wavelength (220 to 280 nm) of UV is effective in killing micro-organisms, and wavelengths close to 253.7 nm are the most effective.
- Radiation from the radiation isotope of cobalt 60 Co, is used as a source of gamma emission.
- Radiation sterilization cause damage to DNA and results in cell death.

- **CONTROLS :**
- Leakers test
- Sterility test
- Clarity test
- Pyrogen test
- **LEAKER’S TEST:**
- It is performed by completely submerging the sealed ampoules in a deeply coloured dye solution.
- Generally 1% **methylene blue** solution is used.
- The ampoules if not sealed properly, the dye solution present outside the ampoules will enter into the ampoules and make the solution coloured.

- CLARITY TEST:
- The parenteral product to be evaluated is placed against a white and black background with the contents set in motion in swirling action.
- It is kept in that motion until any particle becomes visible or not.
- Care is to be taken to avoid any air bubbles.
- **STERILITY TEST:**
- Important to check if the product meets the requirements of sterility according to the official books or not.
- Two methods :

➢The direct transfer of the sample to sterile culture media.

➢The membrane filtration procedure.

- **PYROGEN TEST:**
- Samples of production batch are tested in rabbits for the presence of pyrogens.
- Two stages:
  - Sham test
  - Main test
- **SHAM TEST:**
- If the animals are being used for the first time in pyrogen testing then condition the animals for 1-3 days by injecting 10mg/kg body weight of pyrogen free solution IV.
- Maintain animals like that for 18 hrs in room maintained at a temp of 3 C.
- Record the temperature of the animals beginning at least 90 mins before injection and continuing for 3 hrs after injection.
- Any animal showing variation of 0.6 C or more must not be used for main test.

- **MAIN TEST:**
- Determine the control temperature of each by recording the temperature not more than 30 mins prior to injection of test solution.
- Inject into a ear vein of each rabbit 10ml of the test solution per kg body weight, completing each injection within 10mins after start of administration.
- The test solution must be warmed upto 37±2 C
- Record the temperature at 1,2 and 3 hrs subsequent to the injection.
- Following are the requirements for passing the test:
- Individual rise in temperature of 0.6 C with respect to control and sum of 3 individual rabbits does not exceed 1.4 C, the sample passes the test.
- If anything above the above mentioned requirements, continue the test with 5 other rabbits.
- Individual rise in temperature not more that 0.6 C and sum of all eight does not exceed 3.7 C, the sample passed the test.

PREFILLED SYRINGES

- A prefilled syringe is a single dose packet of parenteral drug to which a needle has been fixed by a manufacturer.
- Prefilled syringes are ready to use disposable syringes contains premeasured dosage, reduce dosing errors and increase patient compliance.
- **PURPOSE OF PREFILLS :**
- The prefilled syringes provides two major purpose to the administration of a drug.
- The first is primary packaging. The purpose of the primary package is to assure that there is no adverse effect on the identity, strength, quality, purity or potency of the drug over its shelf life.
- Second, a prefilled syringe is a delivery system to administer the appropriate amount of the medicament to the patient.

- **TYPES OF PFS SYSTEMS :**
- There are two major types of prefilled syringes systems available :
- Glass-based systems
- Plastic based systems
- **GLASS-BASED SYSTEMS :**
- Traditionally, a prefilled syringe barrel has been made from glass tubing.
- These glass tubes are transformed by heat into the barrel that is used to hold the drug product.
- The benefits of glass systems include:
- Delivers a more accurate dose of the drug to the patient.
- Less pain production at injection site.

- **Drawbacks :**
- Breakage
- Particulate contamination
- Potential surface reactivity
- Dimensional variation

- **PLASTIC BASED SYSTEMS** :
- Plastic based systems are gaining acceptance because of their benefits compared of glass systems.
- The most widely used prefillable plastic syringe systems are manufactured from cyclo olefin polymer (COP) resins.
- **BENEFITS**:
- Break resistance
- Design flexibility
- Compatible with high or low PH.

- MATERIALS USED FOR THE PREPARATION OF PFS:

COMPONENTS	COMPOSITION
Barrel	Glass/plastic
Piston	Elastomer
Tip cap	Elastomer
Plunger	Plastic
Lubricant	Silicone oil
Needle	Stainless steel
Needle	Elastomer
Needle shield cover	Plastic
Finger grip extender	Plastic

- **FILLING PROCESS IN PREFILLED SYRINGES :**
- Newer technique developed by HCM’s (Hyaluron contract manufacturing) patended method of syringe filling involves vacuum filling coupled with online vacuum stoppering, known as bubble-free filling.
- It eliminates the air bubble inside the syringe, (known as “head space”), that results from tradionally filling methods.
- Furthermore, totally removing the gas bubble improves the stability of oxygen sensitive compounds.

- **OPERATION OF FILLING AND STOPPERING:**
- Once the syringe is filling as per the desired volume, the machine stops automatically.
- The operator will keep the plunger nest on the syringe tray.
- Then operator will open the door of stoppering unit (Vacuum chamber) and keep this syringe tray with plunger nest inside the stoppering unit for sealing the syringe and close the door.

- **STERILIZATION OF PREFILLED SYRINGES:**
- Sterilization of prefilled syringe is mainly done by autoclaving or by ionizing radiation.
- Autoclave is not suitable of glass prefilled syringes and normal plastics, as there occurs a PH shift in glass syringes during autoclave sterilization process.
- Mainly used method of sterilization is ionizing radiation.
- Gamma sterilization has proved to be an efficient means of sterilizing prefilled syringes.
- Ionizing radiation has the advantage of sterilization the syringe plunger while they remain in their packaging.

- **SEALING OF PREFILLED SYRINGES:**
- The sequence of nitrogen flushing.
- The plunger die will actuate with the help of pneumatic cylinder and the application of stoppering heads will take place.
- After completion of nitrogen flushing, door gets open itself.
- At the last stage the operator removes the finished prefilled syringes tray with plunger duly placed from the stoppering unit.

- **EASE OF ADMINISTRATION:**
- STEP 1: Verify the label on prefilled syringe as it may be serious if wrongly injected.
- STEP 2: Take out the syringe cap and needle cap without touching the needle tip to prevent the contamination of the syringe.
- STEP 3: Insert the needle . Manually inserting a needle into skin can be a most challenging element of self injection.
- STEP 4: Once injection is completed, the patient must dispose the used syringe.

- **ADVANTAGES AND DISADVANTAGES:**
- The first prefilled syringes were made of polypropylene.
- The advantages of prefilled syringes are:
- **PATIENT RELATED:**
- Reduced risk of dosage error & contamination
- Greater efficiency
- Improved sterility assurance
- Enhanced product differentiation

- **MARKET RELATED:**
- Reduced therapy and injection costs
- Increased market preference.

- **DISADVANTAGES:**
- These are complex medical devices
- Needle stick injuries
- Additional protection required.

NEEDLE FREE INJECTION

- Needle free injection systems are innovative ways to introduce a variety of medicines in patients without piercing the skin. These systems work by the mechanism in which liquid medication is forced at an elevated speed through a small orifice that is held against the skin. Due to this an ultrafine stream of high pressure fluid is created, that penetrates the sin devoid of the use of a needle, thus faster administration of drug occurs as compared to conventional needles.
- **COMPONENTS:**
- Nozzle
- Drug reservoir
- Pressure source

- **MACHANISM OF WORKING:**
- Needle-free injection technology uses force generated by a compressed gas to propel the vaccine at high velocity through a tiny orifice. When administered through the skin, an ultrafine stream of fluid penetrates the skin, delivering the vaccines in a fraction of a second to the skin, subcutaneous tissue, and intramuscular tissue.
- **STAGE 1** : Optimal pressure is used to penetrate the skin (<0.025 sec)
- **STAGE 2** : The delivery or dispersion phase (~ 0.2 sec)
- **STAGE 3 :** The drop-off phase (< 0.05 sec).

- **TYPES :**
- Needle free injection can be divided into **3 types** as per their working mechanism:

➢Powder injection

➢Liquid injection

➢Depot or projectile injection

- Needle free injection devices can be divided into **2 types** based on the source of power:

➢Spring-powered

➢Compressed gas-powered.

- **POWDER INJECTIONS:**
- These injections consists of a chamber filled with solid drug content and a nozzle for firing drug particles into the skin by utilizing the power source which typically is compressed gas.
- The injection has a diaphragm (a few microns thick) on either side of the chamber to cover the drug chamber.

- **LIQUID INJECTIONS :**
- The basic principle of this injection is ‘if a high enough pressure can be generated by a fluid in intimate contact with the skin, then the liquid will punch a hole in to the skin and be delivered in to the tissues in and under the skin.’ Although the same principle is applied as in powder, there is a difference in the actual design and operation of the powder injection devices.
- These systems use gas or spring, pistons, drug loaded compartments and nozzles.
- Typically, the nozzle has an orifice size of about 150 to 300 micrometre.

- **DEPOT OR PROJECTILE INJECTIONS:**
- These systems are designed for administration of a drug into muscles.
- They create a store of drug into muscles that is released continuously over a desired time period.
- **ADVANCES IN NEEDLE FREE INJECTION TECHNOLOGY:**
- Biojector
- Vitajet 3
- Serojet
- Mhi-500
- Lject
- Cool-click
- Recojet

- Intraject technology
- Biovalve’s mini-ject technology
- Antares medi-jector vision technology
- Needle free, auto and pen injectors
- Medajet
- Bioject – zetajet

- **APPLICATION :**
- Mass immunizations
- Intraject technology
- Powderject technology
- Jet injectors technology
- Intradermal delivery landscape

- **ADVANTAGES :**
- Eliminates needle phobia
- Increase patient compliance and vaccination rate
- Elimination of broken needles
- Consistent vaccine delivery
- Higher dispersion pattern
- Elimination of worker needle sticks
- Elimination of needle disposal
- Lower pain and stress.

- **DISADVANTAGES:**
- Higher start-up costs
- Trained personnel
- Lack of worker confidence
- Wetness associated with residual vaccine on the skin surface.

FORM FILL SEAL TECHNOLOGY

- It is an automated computer operated technology, to prepare sterile products like I.V. infusion bottles.
- In this process all steps are performed sequentially, consistently and automatically in a closed sterile chamber of machine such as:
- **FORM – Formulation of container**
- **FILL - Filling of container with content**
- **SEAL -Sealing of container**
- This technology is being used since 30 years and reported to achieve contamination ratee below 0.1%.
- This technique is more popular in U.S. and U.K.

- **RESON BEHIND FFS:**

- The reason behind FFS technology is to reduce the contamination by forming the container, filling the content and sealing in a closed sterile chamber of a machine.
- There is no personnel intervention to reduce the chances of contamination during the manufacturing of sterile products.
- Again it gives more production in very low operational cost with high assurance of sterility.

- **PROCESSING OF FFS:**
- It involves **3** actions:

➢Pre-sterilization of machine

➢Production in aseptic chamber

➢Post-production cleaning.

- **PRE-STERILIZATION OF MACHINE**:
- Pre-sterilization of machine is carried out in **2** different phases:
- **Programmed in sequence:**
- The first is steam sterilization phase consisting of a water steam sterilization cycle at a minimum temperature of 121°C , which will take less than 60 minutes for product tank, filling unit, product pipelines and filling nozzles.

- **H2O2 sterilization cycle:**
- It takes approximately one hour and 40 minutes and it consists in spraying machine tunnel, forming plugs, bell and counter mould, sterilization baths and sterile air pipelines (blowers and diffusers) with hydrogen peroxide fog followed by a drying phase obtained through mechanical dryers and sterile hot air.
- Consequently machine is ready for aseptic packing for continuous up to 48 hours (depending on the product to be packaged) before machine will be cleaned in place.
- Machine sterile conditions are permanently controlled and maintained during the packaging phase by overpressure of sterile air in the feeding tank and all along the closed aseptic tunnel where the filling nozzles are placed.

- **PRODUCTION IN ASEPTIC CHAMBER:**
- This is the heart of FFS technology, which involves 3 working steps:

➢Formulation of container

➢Filling of container with content

➢Sealing of container

- **Formation of container:**
- In this process polypropylene granules are heated at 200 ± 30°C to form parison (a tube like structure). The parison reaches the mould formed the container by the pressure 350 Bar of a sterile compressed air and temperature 170 – 230 °C. Here two halves of the mould closed around the parison to seal the base. Simultaneously the top of the parison is cut free by hot knife edges.

- **Filling of container with content:**
- Bulk solution prepared under aseptic condition is delivered to the machine through a bacteria retaining filter, before entering in container. Fill nozzle (mandrel) fills the liquid in to container with a metered volume of solution, displacing the sterile air. The pipe, filter housing and machine parts that are coming in contact with the product are steam sterilized. Again system uses nylon filter media to remove colloidal silica, pyrogens, mycoplasma, viruses and other contaminants.
- **Sealing of container:**
- After filling the container the filling unit is raised above and the containers are sealed automatically. Then the mould is opened.

- **POST-PRODUCTION CLEANING:**
- After completion of the process the machine is cleaned at the place, means the concept of clean in place (CIP). In this step machine is cleaned at the place where it is installed and should not be transferred to clean room or anywhere else. Again it includes once circulation system and recirculation system. In once circulation system the washed liquid is directly withdrawn from the machine and thrown off. While in case of recirculation system the washed liquid is again re-used to clean the machine and gets recirculated. The machine may be steam sterilized finally.
- FFS machine should be surrounded by class 1,00,000 area. Container formation, filling and sealing process is done in class 100 area within the machine. System should be validated by media fill rums before starting the commercial production.
- This is a fully automated computer controlled technology which allows filling and packing of up 40,000 I.V. bottles per day. N2 purging is available to machine. Sterilization is achieved through an automatic microprocessor controlled circulating water shower. The pressure and temperature link controls the whole process.

- **ADVANTAGES OF FFS TECHNOLOGY :**
- Entire operation takes place in aseptic chamber.
- It reduces personnel contamination.
- A very low manual lab or is required for the operation.
- It gives high production efficiency means about 40,000 I.V. bottles are prepared per day.
- It is cost effective technology for production of I.V. fluid bottles.
- Single machine operates all processes such as formation of container, filling and sealing.

LYOPHILIZATION TECHNOLOGY

- Lyophilization is carried out using a simple principle of physics called sublimation. Sublimation is the transition of a substance from the solid to the vapour state, without first passing through an intermediate liquid phase. To extract water from foods, the process of lyophilization consists of:
- Freezing the food so that the water in the food becomes ice.
- Under a vacuum , sublimating the ice into water vapour.
- Drawing off the water vapour.
- Once the ice is sublimated, the foods are freeze-dried and can be removed from the machine.

- Lyophilization is a process which extracts the Water from foods and other products so that the foods or products remain stable and are easier to store at room temperature (ambient temperature). A Method of drying food or blood plasma or pharmaceuticals or tissue without destroying their physical structure and creation of stable preparation.
- **Traditional Lyophilization Technology:**
- Traditional lyophilization is a complex process that requires a careful balancing of product, equipment, and processing techniques. For nearly 30 years, lyophilization has been used to stabilize many types of chemical components.
- In their liquid form, many such biochemicals and chemical reagents are unstable, biologically and chemically active, temperature sensitive, and chemically reactive with one another. Because of these characteristics, the chemicals may have a very short shelf life, may need to be refrigerated, or may degrade unless stabilized. Heat- and moisture-sensitive compounds retain their viability. Thus, lyophilization ensures maximum retention of biological and chemical purity. Lyophilization gives unstable chemical solutions a long shelf life when they are stored at room temperature

- **PROCESSING :**
- The fundamental process steps are:
- Freezing: The product is frozen. This provides a necessary condition for low temperature drying.
- Vacuum: After freezing, the product is placed under vacuum. This enables the frozen solvent in the product to vaporize without passing through the liquid phase, a process known as sublimation.
- Heat: Heat is applied to the frozen product to accelerate sublimation.
- Condensation: Low-temperature condenser plates remove the vaporized solvent from the vacuum chamber by converting it back to a solid. This completes the separation process.

- **INSTRUMENTATION :**
- The lyophilization equipment
- The environmental conditions necessary for the lyophilization process, sub ambient temperatures and sub atmospheric pressures, are achieved by the lyophilization equipment.
- The following gives a general description of the essential components and their function in a lyophilizer.
- A lyophilizer consists of a vacuum chamber that contains product shelves capable of cooling and heating containers and their contents

- A vacuum pump, a refrigeration unit, and associated controls are connected to the vacuum chamber.
- Chemicals are generally placed in containers such as glass vials that are placed on the shelves within the vacuum chamber.
- Cooling elements within the shelves freeze the product. Once the product is frozen, the vacuum pump evacuates the chamber and the product is heated.
- Heat is transferred by thermal conduction from the shelf, through the vial, and ultimately into the product.

- **RECENT ADVANCES IN LYOPHILIZATION EQUIPMENTS:**
- Equipments used in **large scale** production :

➢Freeze dryer scitek

➢Sterile steam production freeze dryer Mill rock

- Equipments used in **small scale** production :

➢Benchtop Pro freeze dryer

➢Freezemobile Freeze Dryer

➢Vaccum concentrator

- **EQUIPMENTS USED IN LARGE SCALE PRODUCTION:**
- **FREEZE DRYER SCITEK:**
- It offer cGMP vacuum freeze drying equipment for the reliable lyophilization of a wide range of pharmaceutical and biotech products.
- **STERILE STEAM PRODUCTION FREE DRYER MILL ROCK:**
- **Temperature Range-**60C to +65C (+80C option.)
- **Shelf Heat Transfer** Hollow Fluid Fill.
- **Shelf Area**8 sq ft to 10 sq ft.
- **Shelf Assembly** Bulk or Hydraulic Stoppering.
- **Condenser Temperature -**75 C.

- **Chamber Configuration** Cylindrical or Rectangular.
- **Condenser Style** Coil or Plate.
- **Defrost** Steam.
- **Vacuum Pump** Leybold Rotary Vane or Dry Pumps.
- **Vacuum Control** Capacitance Manometer with Solenoid/Needle Valve.
- **EQUIPMENT USED IN SMALL SCALE PRODUCTION:**
- **BENCH TOP PRO FREEZE DRYER:**
- Key features :
- Compact, bench-top design
- Available in 3, 8 and 9 liter configurations
- Direct chamber, flask and/or rack drying capabilities

- PLC-based Omnitronics controller
- Choice of refrigeration system to meet various process requirements
- Optional manifolds, racks and accessories available
- **ADVANTAGES:**
- Benchtop freeze dryers with temperature-controllable shelves similar to those on larger systems.
- The precise freeze-drying control is ideal for processing valuable or sensitive biological materials or developing safe, repeatable processes.
- It is ideal for pilot or R&D laboratories that need a more advanced level of process control but lack the space for free-standing research systems.

- **FREEZEMOBILE FREEZE DRYER:**

- Freeze mobile freeze dryers are designed with flexibility and convenience in mind.
- A broad selection of multiple users to configure the same system for a wide range of different applications.
- With an optional shell freezing bath and a wide range of single and multi-tier horizontal “T” type manifolds the Freeze mobile can dry multiple flasks simultaneously.

- **VACUUM CONCENTRATORS:**

- Concentration can be a tedious laboratory procedure, so the miVac features several innovations designed to speed up concentration times.
- The miVac Speed Trap is radically different from traditional cold traps.
- The cold condenser coils are suspended directly in the vapour path, enabling the condensed solvent to run off into the jug without freezing and causing a decline in the condensing power of the coils.

- **RECENT ADVANCES AND FURTHER CHALLENGES IN LYOPHILISATION:**
- Lyophilization beyond drying of pharmaceutical proteins.
- Pharmaceutical applications of lyophilizates in the solid state.
- Novel formulation aspects.
- Importance of the freezing step in lyophilization.
- Lyophilization above Tg. (glass transition temp. of the maximal freeze concentrate)
- Stabilization by thermal treatment/ high secondary drying temperatures.
- Individual factors contributing to protein stability during Lyophilization.

- **ADVANTAGES:**
- Minimum damage and loss of activity in delicate heat-liable materials.
- Speed and completeness of rehydration.
- Possibility of accurate, clean dosing into final product containers.
- Porous , friable structure.
- **DISADVANTAGES:**
- High capital cost of equipment.
- High energy costs.
- Long process time(typically 24hr.drying cycle).

- **USES:**
- Use of lyophilization for the pre-treatment of samples and standards prior to their storage and/or pre concentration is presented.
- It is often used to prepare dry pharmaceutical formulations to achieve commercially viable shelf lives.
- **APPLICATION:**
- Lyophilization maintains food/biochemical and chemical reagent quality.
- Lyophilization greatly reduces weight, and this makes the products easier to transport.
- Pharmaceutical and biotechnology

LARGE VOLUME PARENTERALS

- The USP provides the definition for large volume parenteral (LVP’s) the large volume solution applies to an injection that is intended for intravenous use and is packaged in containers holding 100ml or more.
- LVP’s means a sterilized aqueous drug products packaged in a single dose container with a capacity of 100ml or more.
- It included IV infusions, irrigating solutions, peritoneal dialysates and blood collecting units with anticoagulant.

- **CHARACTERISTICS OF LVPs:**
- Packaged in glass bottles or in large volume flexible containers.
- May contain greater than 100ml to greater than 1 or 2 L
- Sterile
- Pyrogen-Free
- Isotonicity
- Essentially free of particulate matter.

- **FORMULATION:**
- Water for injection
- Inorganic salts
- Carbohydrates
- Nitrogen containing substances
- Buffers
- Tonicity modifiers
- Antioxidants
- Antimicrobial agent

- **PRODUCTION:**
- **QUALITY AND STABILITY:**
- The quality of the starting materials and solutes is critical to the finished LVP’s product.
- Presence of contaminants or degrades that effect finished product are considered.
- Heat, light, moisture and air can adversely effect many of these materials.
- The containers for these drug substances can also be imp factors in stability considerations.

- **RECEIVING:**
- A specific, isolated area is usually dedicated as a delivery point for the receipt of raw materials. All raw materials must be inspected, identified, documented and sampled in accordance with written procedures.
- Materials should be received covered or in closed containers.
- **STORAGE AREAS:**
- All materials associated with the final drug products must be sampled, distributed to laboratory functions.
- Labels on materials.

- **BATCH MIXING:**
- The majority of LVP’s are simple aqueous solution. The process for manufacturing simple LVP’s is straight forward, since the solutes are readily soluble in water.
- The solution mix tanks are made of stainless steel and are fitted with agitators to provide a uniform concentration throughout the contents.
- Some solutions may require heat to effect dissolution of the solutes.
- For example:

➢Solutions that are very concentrated or solutions where solutes have low solubility.

- Jacketed mixing tanks are used.
- These tanks also have temperature monitoring devices to monitor the temperature of the solution.

- **IN-PROCESS ASSAYS:**
- In-process assays may be performed for one or more ions or other substances and adjustments in solute concentrations made as required before dilution to final prescribed volume.
- Analytical methods performed as in-process assays must be precise and accurate.
- **FILTRATION:**
- Filtration may be defined as the separation of undissolved particles from a liquid by passing a solution through a septum or porous medium that allows the liquid to pass but retains the particles.
- The filtration of liquids is one of the most important operations in pharmaceutical technology. Originally, liquid products were filtered to improve their clarity and pharmaceutical elegance.

- The rate of filtration can be measured as the volume (mass) of fluid passing through the filter in a unit of time .
- Membrane filters, screen filters, cake filters, depth filters are used for this filtration process.
- **CLEANING PROCESS EQUIPMENT :**
- WATER SYSTEMS: Study of microbiology of water is imp, because water is used for cleansing the equipment before and after manufacture of parenterals.
- Mostly gram-negative org’s like coliform bacteria, pseudomonas, Xanthomonas, flavobacterium are water born and these are killed by autoclaving.
- All the parts of the equipment should be disassembled, sanitized, cleaned, thoroughly rinsed with water, dried, and inspected for leaks before reassembly.

- **CONTAINERS AND CLOSURES:**
- **GLASS CONTAINERS:**
- Glass containers have been employed for LVP’s. solid rubber stoppers are used for the container closure systems.
- Because of weight and fragility, the glass containers have been largely replaced by plastic. Glass is used only for solutions which are basically incompatible with plastic.
- Washed, cleaned glass containers should be held at a minimum of 70°C to supress microbial growth.
- Removal of pyrogens from the containers are by subjecting them to a temperature of 210°C for 3-4 hours or 650°C for 60 seconds.

- **TYPES OF GLASS:**

- **TYPE I** : Commonly known as neutral glass. It has a high resistance to hydrolysis withstands autoclaving, weathering and solution of PH of up to 8.
- **TYPE II** : Containers may be treated with moist sulphur dioxide at high temperature to create a neutral surface film with high hydrolytic resistance. Lower resistance to autoclaving than for type I glass.
- **TYPE III** : This offers very little resistance to hydrolysis and should only be used for powders for reconstitution prior to injection and for non aqueous preparations.

- **PLASTIC CONTAINER:**
- **BASIC TYPES OF PLASTIC:**
- **Thermoplastics:**
- Polymers that soften upon heating and solidify upon cooling.
- Most parenteral packaging
- **Thermosets:**
- Chemically reactive polymers in the fluid state.
- Harden irreversibly by cross-linking.
- Epoxies, melamine resins, cross-linked polyesters.

- **MOST COMMON POLYMERS FOR STERILE PRODUCTS:**
- Polyethylene (PE)
- Polyvinylchloride (PVC)
- Polypropylene (PP)
- Polyamide (Nylon)
- Polycarbonate (PC)
- Ethylene vinyl acetate (EVA)
- Polyolefin (mixtures of low density PE, high density PE, PP, and EVA)