

Industrial Pharmaceutical Regulation

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Course Outline

- Course objective
 - This course is designed to provide understanding on the aspects of drug manufacturing, which encompasses the processes involved while observing drug regulation and standard practice
 - The course will provide students with the knowledge and basic understanding on the requirement for different kinds of processes and techniques employed in drug manufacturing, depending on suitability for drug delivery and means for assessing the quality and properties.



Course Assessment

- Assignment 10%
- Quizzes 10%
- Mid semester examination 35%
- End of semester 45%



Learning Outcome

- Student will be able to:
 - Describe the requirements for drug manufacturing.
 - Describe production process operations, machinery/equipment involved and current techniques employed in quality control.
 - Explain legal and regulatory aspects in ensuring the production of quality and effective drugs.
 - Explain other aspects of industrial pharmacy including statistics on clinical trials, quality control and drug stability monitoring



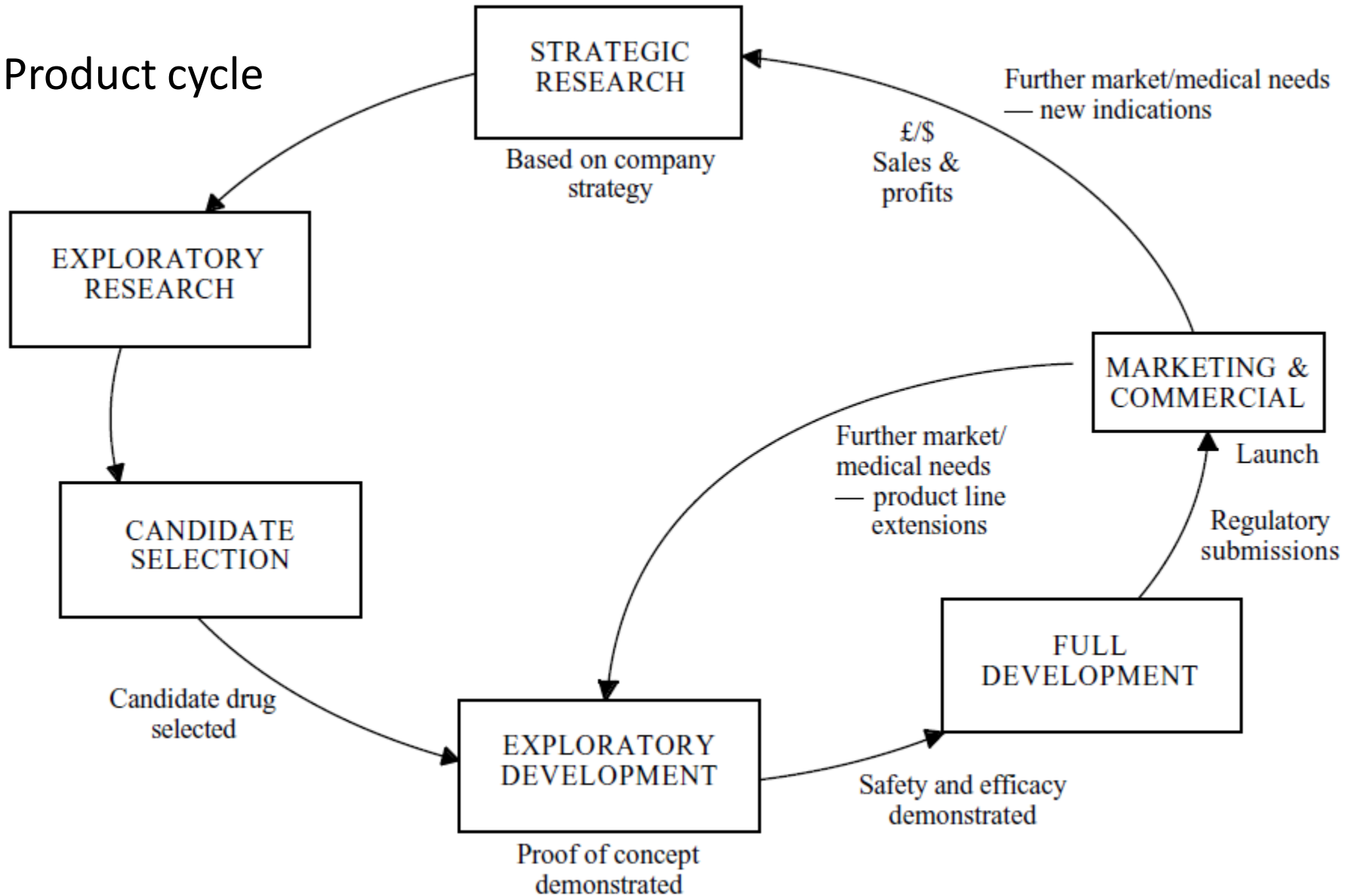
Topics

- Manufacturing processes
- Design and dosage forms
- Preformulation, Biopharmaceutics
- Processing of powders and compaction
- Sterilisation
- Processing of liquids
- Drug stability
- Clinical trials
- Design and operation of clean rooms
- Environment packaging
- Quality control/assurance
- GMP
- Pharmaceutical regulation



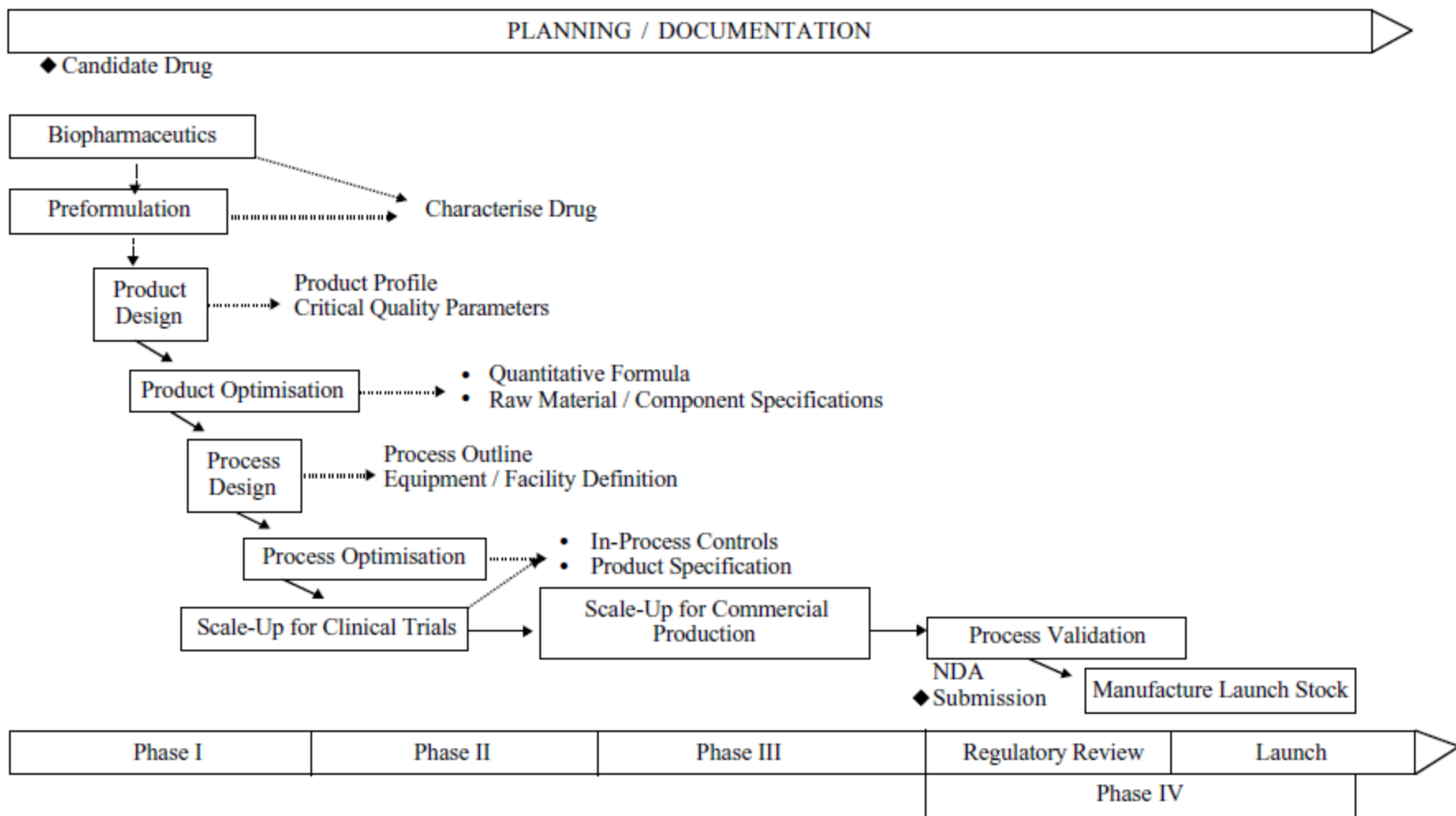
Introduction

Product cycle



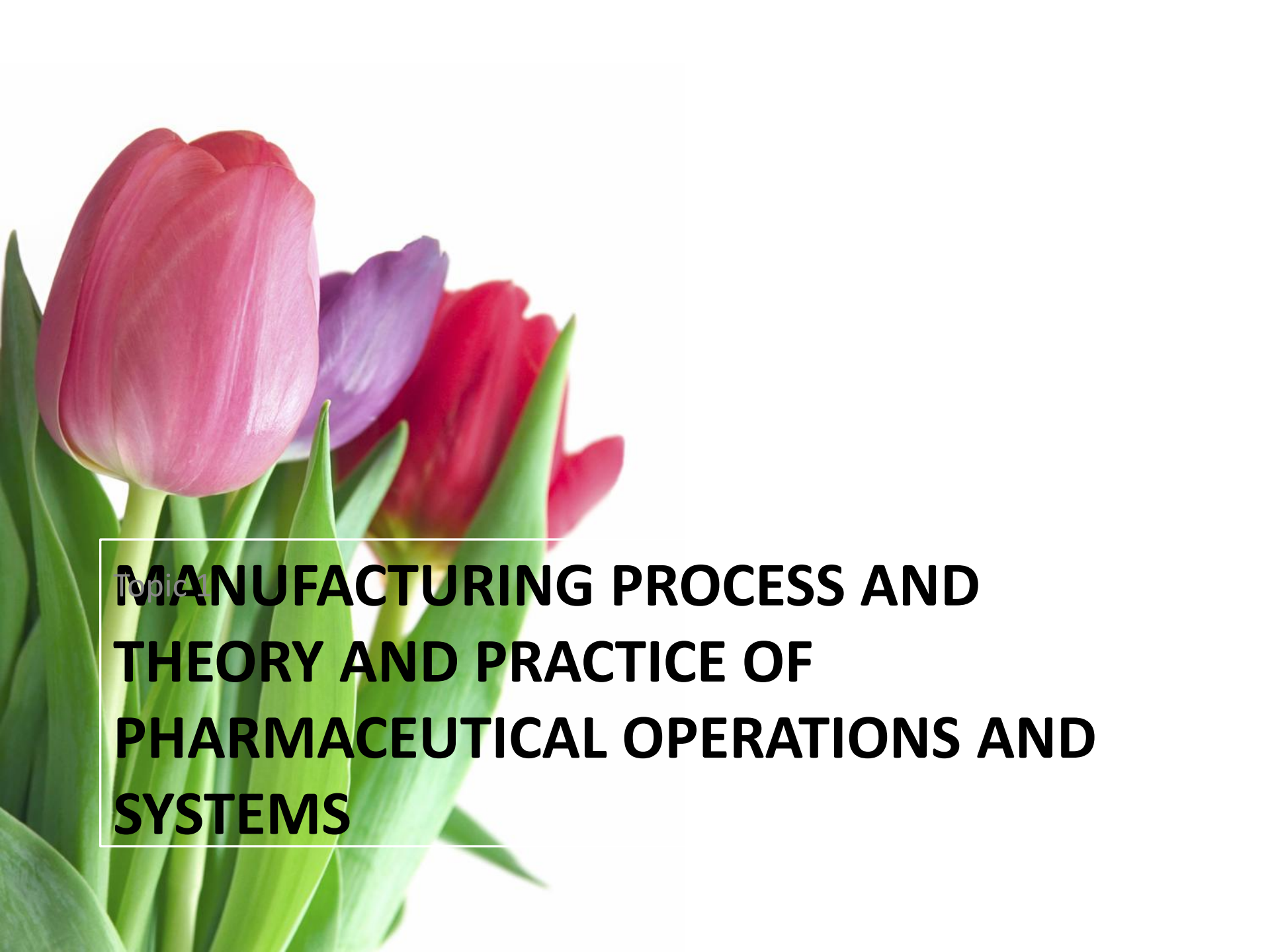


Framework for product development





- The quality of the design activities can strongly influence the success of development of the right product to the market and ultimate return on investment



Topic 1

MANUFACTURING PROCESS AND THEORY AND PRACTICE OF PHARMACEUTICAL OPERATIONS AND SYSTEMS



- The selection of manufacturing methods for pharmaceuticals is directly related to the means by which the active substance is brought into contact with the agent responsible for the illness
- Process in pharmaceutical industry:
 - Testing libraries of new chemical compounds
 - Laboratory screening
 - Clinical investigation or trial
 - FDA's approval
 - Manufacturing process
 - Distribution



- **Principle of GMP**

pertaining to process

- Follow defined procedures.
- Comply to principles of GMP
- Aim for products with quality attributes in accordance with the marketing authorisation

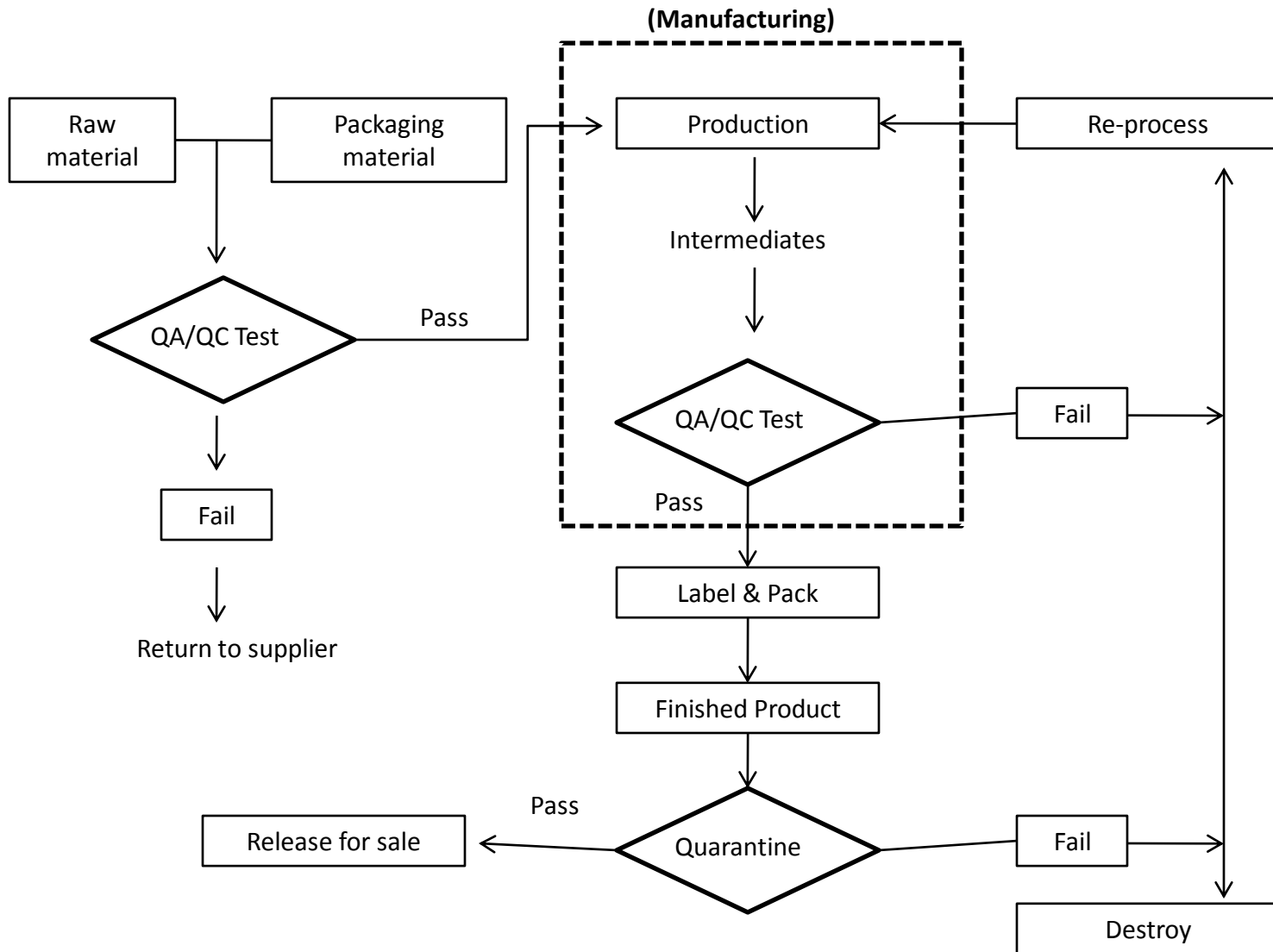


- What is a Process?

Protocol or procedure or method; a series of steps to accomplish a desired result/final product



Basic Process Flow





Type of processes

- Sterile/non sterile
 - require different environmental specs
- Liquids dosage forms
 - liquid, syrup, suspension, lotion, etc.
- Semi solid dosage forms
 - cream, ointments
- Solid dosage forms
 - tablets, capsules, pills, powders
- Special forms
 - coating
 - aerosol inhalers
 - softgel
 - transdermal patches



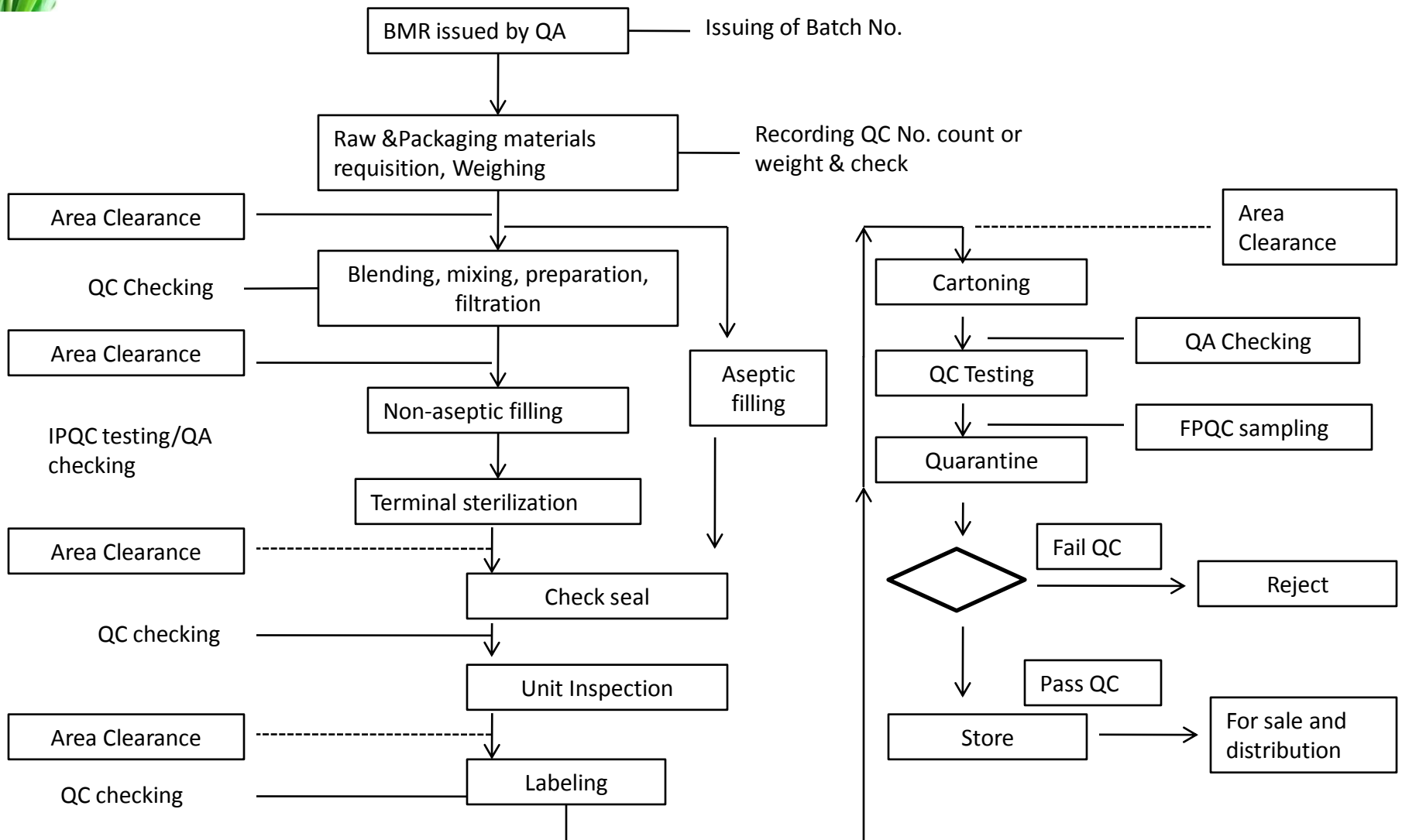
Sterile Processing

- Hence, if a medicinal substance has poor stability in acid solution or is easily broken down by digestive enzymes, it is of very little use in disease control as it will probably not reach those parts of the body's systems requiring treatment.
- The sterile product manufacturing system includes measures that minimize the hazard of contamination with microorganisms and particulates of sterile drugs.



- High degree hygiene practice and GMP compliance
GMP compliance basic:
 - Personnel
 - Building
 - Air
 - Environmental control
 - Water for injection
 - Container and closure
 - Sterilisation
 - Personnel practice
 - Laboratory control
- In-process monitoring compulsory. Aseptic technique employed for non terminal sterilized and at critical process (eg. filling). High preferable: terminal sterilization

Sterile production-Process Flow



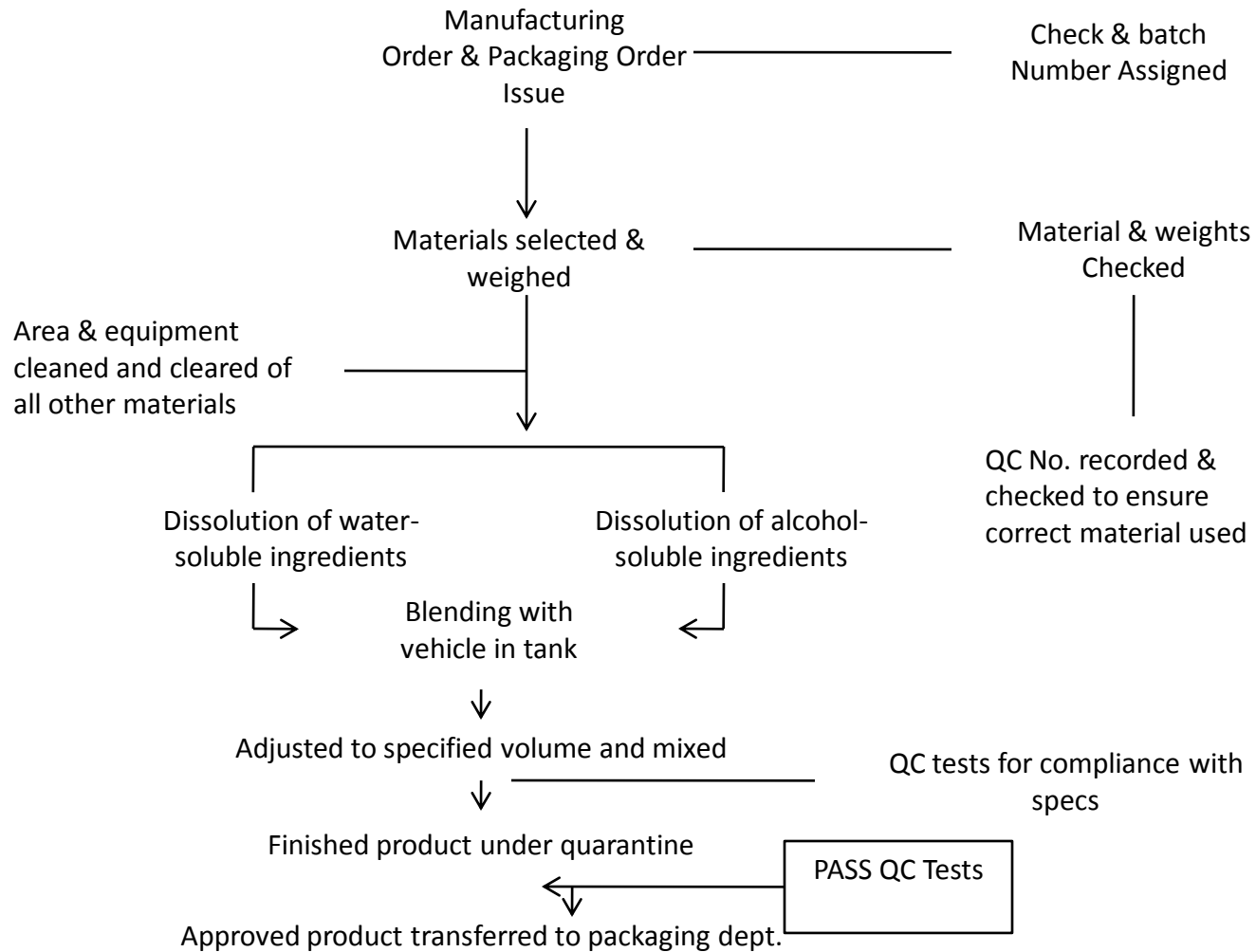


Liquid Processing

- Liquid processing involves blending drug and excipients into a liquid phase
- Critical issues are:
 - Physical: colour, appearance, taste
 - Chemical: pH, viscosity
- Transfer of product is easy and filling into immediate container is critical and high risks of microbial problems
- Filtration prior to filling avoid presence of visible foreign matters



Flow chart of Liquid Manufacturing

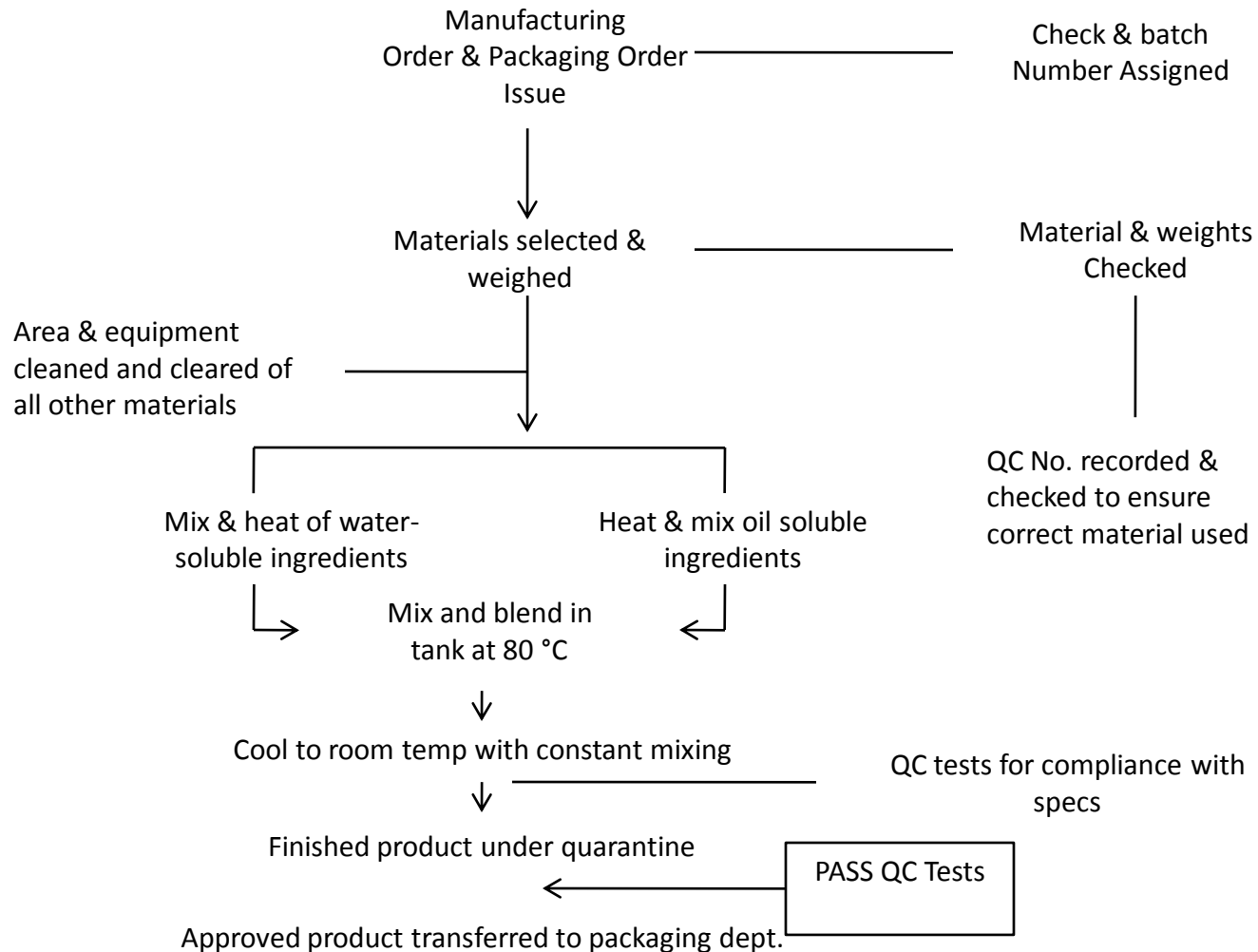




Semi-solid processing

- Mixing of liquid phase and oily phase
- Oily phase usually in hard form and require prior melting before blending
- Use of heat to melt and mix in formation of a homogenous mix
- High risks of microbial problems
- Transfer is difficult
- Critical issues are:
 - Physical: colour, appearance
 - Chemical: pH, viscosity, microbial content

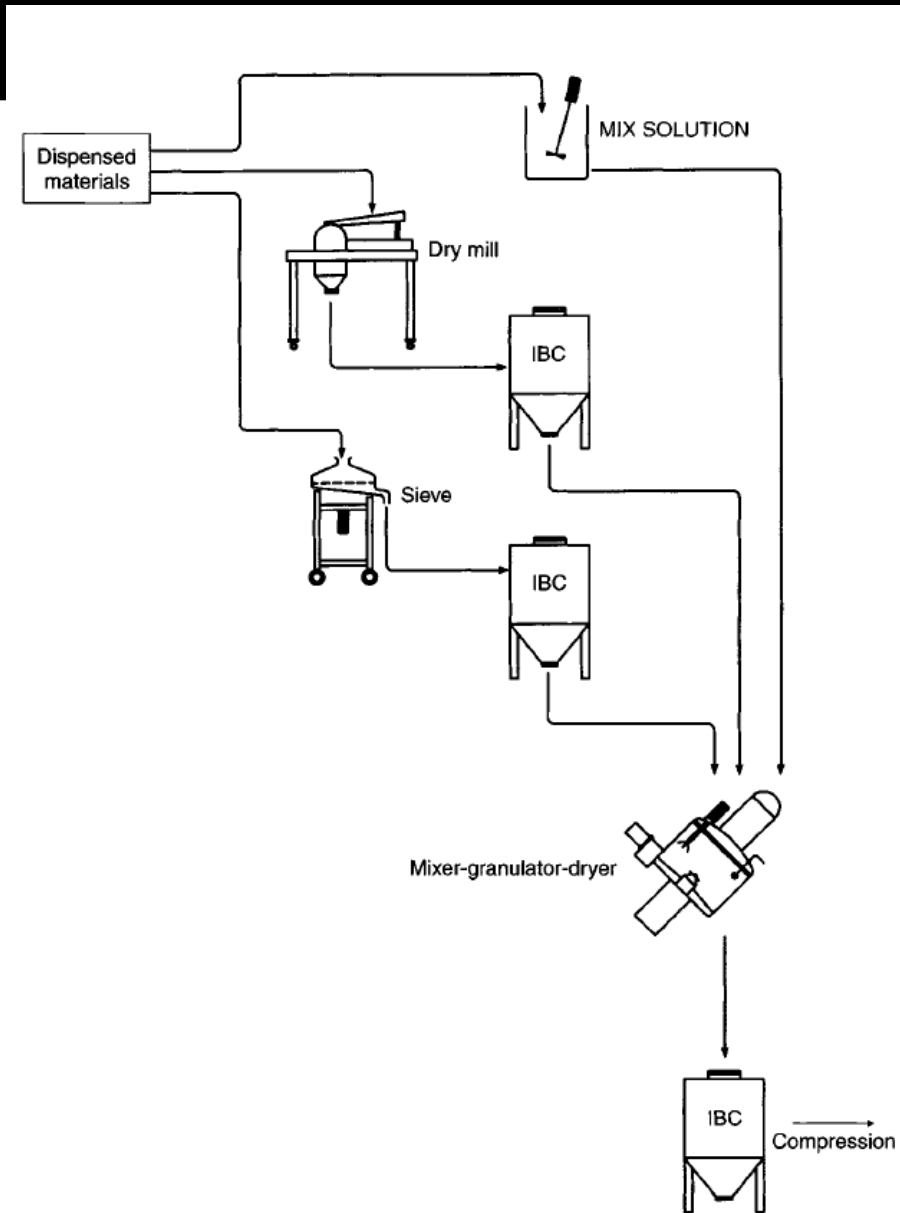
Flow chart of semi solid manufacturing



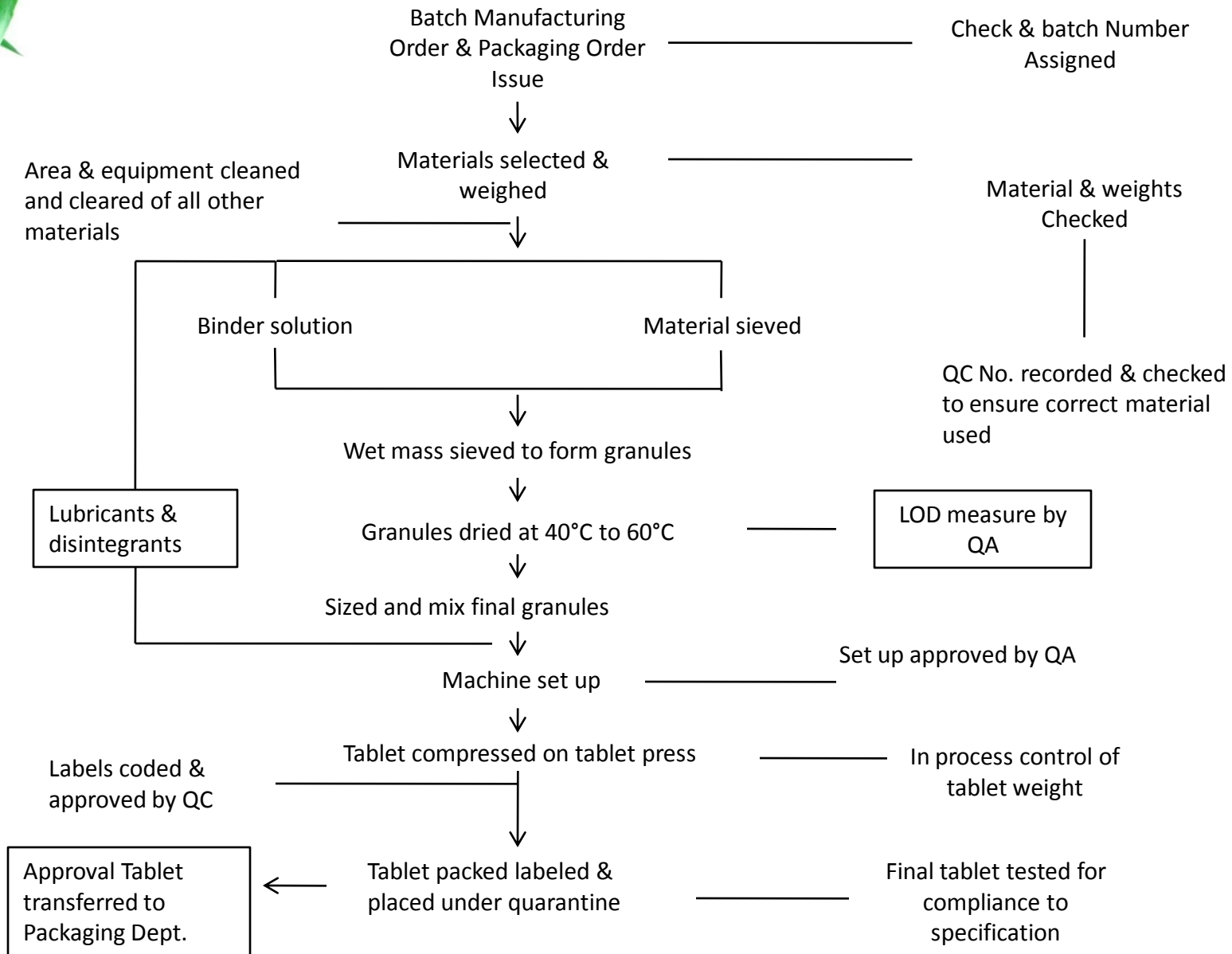


Solid Processing

- May be wet (granulation)-require drying
- Dry processing (direct mixing, direct compression)
- Require particle size control; use of sieving and mills prior to mixing is common
- Process is dusty-require dust control
- Transfer is difficult, mix must be “flowable”
- High risk of cross contamination
- Low risk of microbial problem

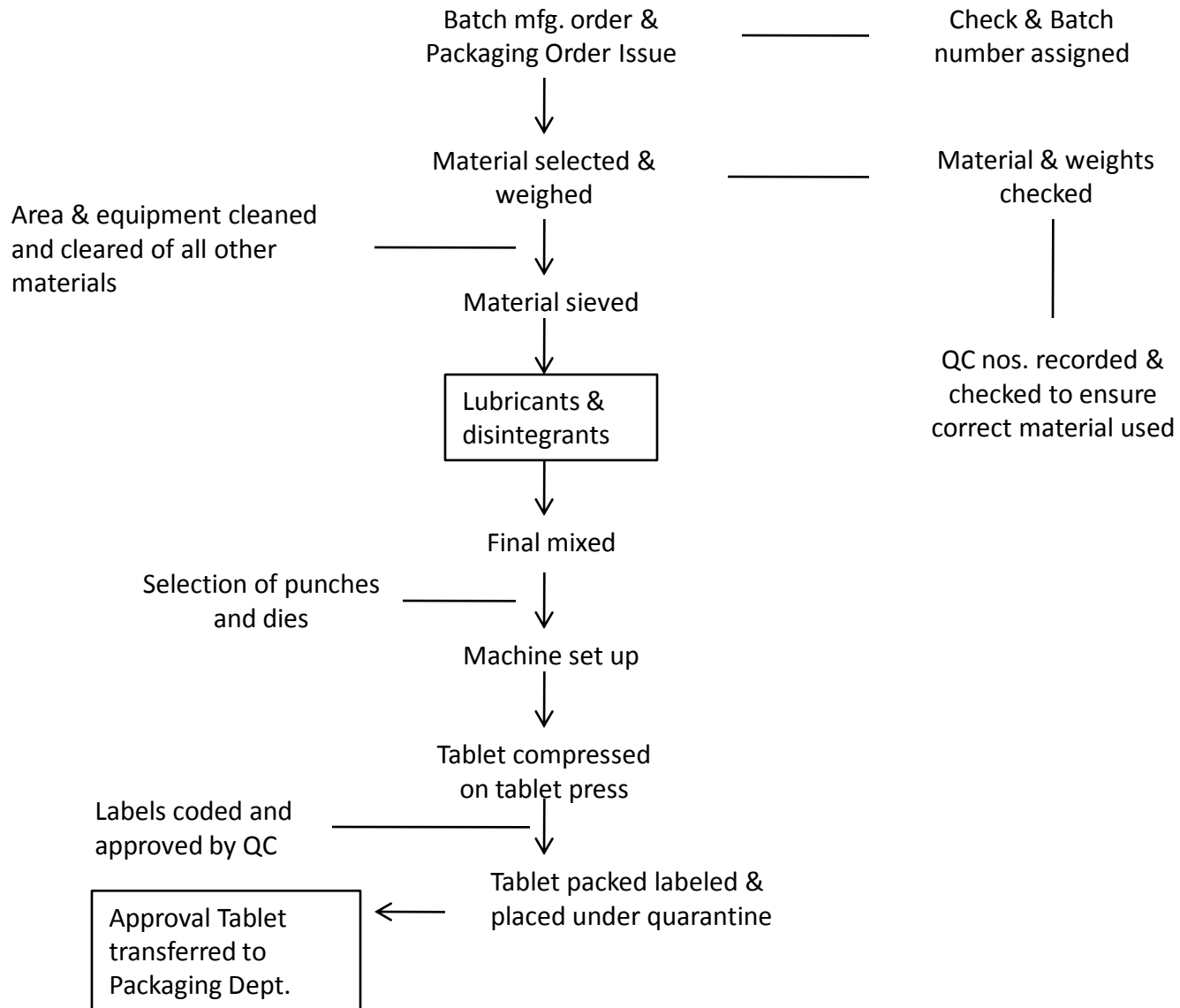


Flow chart of tablet manufacturing process (Wet granulation)





Flow chart of tablet manufacturing process (direct compression)





Special processing

- Coating
 - Normal coat, enteric, controlled release, etc.
- Softgel –dedicated equipment for formation of capsule gel and filling into capsules. Same with filling liquid into hard shell capsules
- Aerosol –powder/aerosol form. Require dedicated equipment and use of propellants
- Transdermal patches –specially designed equipment for preparation of patches and storage of products on patches



Packaging operation

- Minimize risk of contamination, mix-ups or substitutions. (No packaging of different batches in close proximity)
- Conduct line clearance before start as per written SOP
- Identification of packaging line by product detail
- All primary container must be pre-cleaned and inspected for absence of foreign matter
- Special attention and caution in printing & coding activities (Need line clearance too)
- Upon completion, reconciliation of materials to be done and recorded. Any discrepancy to be investigated, corrected and approved



Packaging operation

- In process control should includes:
 - Physical appearance
 - Completeness of packages
 - Correct material used
 - Correct coding
 - Correct functioning of checking instruments
- Checking instruments: electronic code readers, weight checkers, label/product counters, label checkers, etc. to be checked in IPQC
- Products rejected and re-introduced after rectification require approval from authorized personnel (via a written procedure) and be documented.



Product/material status

- Quarantine
 - pending approval
- In-process
 - WIP
- Passed
 - released/approved
- Re-processed
- Rejected



Re-processing (re-work, re-do)

- Require a written procedure and be documented
- Limitation:
 - Product safety & quality not affected
 - FPQC specs met
 - Follow written procedure
 - Approved by authorized person
 - Evaluate potential risks and take measures
- May require additional testing
- Evaluate effect on shelf-life



Process Validation

- Definition

The documented evidence that the process, operated within established parameters, can perform effectively and reproducibly to produce a medicinal product meeting its pre-determined specifications and quality attributes



- Process validation: key word to definition
 - Action
 - Documentation
 - Process or methods
 - Perform effectively
 - Reproducible
 - Produce products that meet predetermine specifications



- Validation is a documented program
- Leads to understanding of causes of variation in the process
- Enables:
 - To qualify critical processes
 - To qualify support processes
 - To establish critical process variables
 - To set limits for process control



In-process control (for process)

- Line clearance
- Check during dispensing
- IPQC of intermediate
- Check on yields & reconciliation of materials
- Checks on piping, hoses & connections
- In process controls methods & its results to be approved by QC



In Process Control

- Compulsory for all critical process
- IPQC ensure process complies to set predetermined specification
- Checks done while process on going
- Done by operator and/or QA personnel
- IPQC requires control limit and reference
- Deviation will require a SOP on action to be taken
- IPQC result always used in evaluation of final product for quarantine release



In Process Control

- Checks on yield & reconciliation of materials
- In-process quality control (IPQC) should includes:
 - Physical appearance
 - Completeness of packages
 - Correct material used
 - Correct label & coding (identity)
 - Correct functioning of checking instruments



- Main IPQC activities are:
 - Area (line) clearance
 - Yield control
 - Reconciliation
 - Use of GMP status
 - IPQC of various dosage forms



Line clearance

- Done before start of a process
- Ensure identification, correct materials and equipment used
- Check on setting of critical parameters
- Absence of 'foreign' matter
- Hygiene, cleanliness and GMP compliance
- Suitable environmental parameters
- Avoid potential parameters
- Avoid potential risk of mis-labeling and mix-up



- Some basic rule for Line clearance
 - Removal of all previous product from the area & machines
 - Removal of all waste from the area and machines
 - Reconciliation of all printed material & product from the previous batch
 - Cleaning of the area & the machine
 - Verification of environmental parameters
 - Verification record that the area and machine have been inspected and found to be clear of all previous product



- To check:
 - Area/room
Floor, wall, ceiling, temperature, absent of previous batch etc.
 - Equipment
Surface cleanliness, no previous product label. Surfaces must be dry, correct setting, etc.
 - Personnel
Healthy, hygiene, understand the job given etc.



- Documentation
 - Area clearance form
TO BE FILLED BY Line-leader; check by Supervisor/above.
Approved by Production Executive/above
 - Log book (room & machine)
To be filled by operator; check by Line leader/above



Yield Control

- Done at end of a stage/process
Check on yields, reconciliation on quantities to be carried out
- Require control limits based on previous record and/or validation
- Theoretical target is 100% yield
- Set a realistic target for yield and justify it
(based on product dosage form, ease of process, batch sizes, pack sizes, etc)



Yield Control

- Deviation from set yield target require initiation of investigation and corrective action. This to be documented
- Calculate yield on end of each stages. Results should fall within pre-determined specification
- As a mean of 'reconciliation' for intermediates and finished products
- Based on theoretical yield and actual yield



Yield control

- Target for yield depends on dosage form and difficulty of processing
 - For dry products, usually 95.-100%
 - For liquids, 95-102.5%
 - For capsules, 90-100%
 - For herbal capsules, 85-100%
- Out of specs (OOS) value warrant investigation:
 - Fear of mix-up or sabotage
 - Possible pilferage by internal staff
 - Check for unusual wastages



Yield Control

- Theoretical yield 10,000 bot – T
 QA sample 25 bot – b
 Amount for sale 9,500 bot – c
 TOTAL 'manufactured' 9,525 bot – A

$$\begin{aligned} \text{Yield (Y)} &= (A/T) \times 100 \\ &= (9,525/10,000) \times 100 \\ &= 95.3\% \end{aligned}$$

Target yield is 95% - 102.5%

Yield is within specification. This is acceptable



- E.g of yield formulation

Batch quantity = 100 kg

Weight per tab = 500.0 mg

Pack size per Unit = 100 tabs

(T) Total theoretical yield 100 kg x 1000/unit wt (g) = _____ total units

(A) Actual No. of unit produced = 1,900 units

(R) No of rejects = 70 units

(Q) QA samples = 20 units

Production Yield = $(A+Q)/T \times 100\% =$ _____%

Rejects = $R/T \times 100\% =$ _____%

Calculate production yield and rejects . Is process acceptable?



Reconciliation

- Definition

A comparison, making due allowance for normal variation, between the amount of product or materials theoretically and actually produced or used



Reconciliation

- Check on yields, reconciliation on quantities to be carried out
- Reconcile material used. This is to ensure every materials is being used, no 'stray' material or no 'outside' materials added.
- Reconciliation particularly critical for intermediates and printed material



Reconciliation

- Useful tool for quality assurance
- Need written procedure (SOP) for executing reconciliation
- Mainly done on packaging materials, especially printed labels, leaflets and boxes, although better if can do on intermediates too.
- Non-reconciliation (or discrepancies) will warrant or require an investigation be initiated, root cause identified and corrective action done, before the batch can be released
- Investigation may affect other 'adjacent' batches
- Resume of process only by an authorized person



Reconciliation

- Activity to be recorded and verified
- Ensure correct materials/labels are used
- Ensure no 'strayed' materials/labels
- Ensure no substitution from other materials
- Prevent no-labels of finished product
- Prevent mis-labeling of products
- Ensure no pilferage or sabotage by personnel



Reconciliation

- Non-Reconciliation

Quantity issued	1650 – a
Quantity used	950 – b
Quantity rejected	120 – c
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Quantity returned	530 – d
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TOTAL	1600 – T

When $(a) \neq (b) + (c) + (d)$, Reconciliation is NO



reconciliation

- Reconciliation

Quantity issued	1650 – a
Quantity used	950 – b
Quantity rejected	150 – c
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Quantity returned	550 – d
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TOTAL	1650 – T

When $(a) = (b) + (c) + (d)$

Reconciliation is YES



Use of GMP Status

- Control by status labels (colour coded)
- For materials (raw & packaging), intermediates and finished products
- **Quarantine** (review all processing records before release)
- **Reject**
- **Pass**
- None without status allowed within premise
- Avoid product mix-up and 'adulteration'



Use of GMP Status

- Prevention of cross-contamination with other products, foreign matters and microorganism
 - Proper status label & identification of all materials, intermediate and products at every stages so as to prevent mix-up
 - At all time during processing, rooms used should also be labeled or identified with an indication of the product or material being processed, its strength, batch number and stage of production



- In-process control is required to minimize the possibility of extraneous contamination, cross contamination, inferior or defective quality, mix-up, mislabeling or incorrect identity of product that can cause hazardous effect to the consumer and worst, can cause death.