

PHARMA BOOK BY SIMPAL BARIA



INDEX

SR. NO.	CONTENTS	PAGE NO.
1.0	SITE MASTER FILE (SMF)	6
2.0	VALIDATION MASTER PLAN (VMP)	7
3.0	QUALITY MANUAL (QM)	8
4.0	CHANGE CONTROL	9
5.0	DEVIATION	13
6.0	MARKET COMPLAINT	18
7.0	PRODUCT RECALL	29
8.0	CAPA	32
9.0	MANAGEMENT NOTIFICATION	34
10.0	NPI	35
11.0	REGULATORY UPDATES	36
12.0	PLANT QUALITY REVIEW MEETING	37
13.0	SHELF INSPECTION	38
14.0	VENDOR MANAGEMENT	39
15.0	CLEANING VALIDATION	43
16.0	PRODUCT QUALITY REVIEW (PQR)	51
17.0	PROCESS VALIDATION	54
18.0	QUALITY RISK MANAGEMENT	57
19.0	STABILITY STUDIES	66
20.0	ANALYTICAL METHOD VALIDATION	70
21.0	OUT OF SPECIFICATION	79
22.0	MICRO	84

INDEX

SR. NO.	CONTENTS	PAGE NO.
23.0	TRAINING	87
24.0	MEDICAL CHECKUP	89
25.0	PEST CONTROL	89
26.0	RODENT CONTROL	90
27.0	HEALTH	90
28.0	HYGIENE	91
29.0	QUALIFICATION	92
30.0	HVAC SYSTEM	94
31.0	RLAF/LAF	107
32.0	WATER SYSTEM	109
33.0	COMPRESSED AIR	131
34.0	ENGINEERING	139
35.0	PREVENTIVE MAINTENANCE	147
36.0	CALCULATION	147
37.0	PHARMACODE	148
38.0	SAMPLING PROCEDURE	152
39.0	OUT OF TREND	154
40.0	EQUIPMENT CLEANING PROCEDURE	154
41.0	PUNCH AND TOOLING	156
42.0	DIFFRENCE BEWTWEEN MOISTURE CONTENT AND LOD	166
43.0	DIFFRENCE BEWTWEEN CALIBRATION, VALIDATION AND QUALIFICATION	166
43.1	CALIBRATION, VALIDATION AND QUALIFICATION	166

INDEX

SR. NO.	CONTENTS	PAGE NO.
43.2	DIFFRENCE BEWTWEEN OOS AND OOS	167
44.0	DIFFRENCE BEWTWEEN CHANGE CONTROL AND DEVIATION	167
45.0	DIFFRENCE BEWTWEEN SOP AND PROTOCOL	167
46.0	CHANGE ROOM AND LINE CLEARANCE CONCEPT	168
47.0	BATCH RECORD	169
48.0	PASS BOX	170
49.0	EQUIPMENT AND PROCESS	171
50.0	BALANCE CALIBRATION	203
51.0	IPQA	204
52.0	ONLINE SYSTEM FLOW	215
53.0	SAP	216
54.0	HOLD TIME STUDY	218
55.0	MVTR	221
56.0	HANDLING OF LABORTORY INCIDENT / DISCREPANCY	223
57.0	CONTRACT TESTING LABORATORY	225
58.0	RELEASE OF INTERMEDIATE AND FINISHED PRODUCTS	227
59.0	FAILURE INVESTIGATION AND ROOT CAUSE ANALYSIS	230
60.0	HANDLING OF PHARMACOPEIAL CHANGES	238
61.0	GOOD MANUFACTURING PRACTICES (GMP)	240
62.0	21 CFR (CODE OF FEDERAL REGULATIONS)	241
63.0	ICH (INTERNATIONAL CONFERENCE HARMONIZATION)	242
64.0	SCHEDULE M	245

INDEX

SR. NO.	CONTENTS	PAGE NO.
65.0	VARIATION FILE	249
66.0	CLINICAL TRIALS	253
67.0	MARKETING AUTHORISATION	257
68.0	EUDRALEX	262
69.0	SUPAC	265
70.0	EDQM	267
71.0	ORANGE GUIDELINE (MHRA)	268

PHARMA BOOK

SR. NO.	QUESTION ANSWER
1.0	**SITE MASTER FILE (SMF)**
1.1	**What is SMF** Site Master File is Full information about the site. Site Master file is a document that summarises the firm's overall philosophy, intentions and approach to be used for establishing registration in various countries.
1.2	**Which Guideline follow for preparation of SMF** PIC/S and EU Guideline (Eudralex Volume-4).
1.3	**Preparation** SMF is Prepared by Quality Assurance and Reviewed by Plant Head and Authorised by Head QA.
1.4	**Contents of SMF** 1. General Information 2. Personnel 3. Premises and Equipment 4. Documentation 5. Production 6. Quality Control 7. Contract Manufacture and Analysis 8. Distribution, Complaints and Product Recall. 9. Self Inspection
1.5	**Review Period** Any changes after approval of SMF shall be recorded in **Annexure-II** for keeping a track of changes taken place. All such changes shall be collated and amended in the next revision. Site Master File shall be revised at end of every calendar year or as and when required through change control management system
1.6	**Storage Period** Site Master File shall be store by QA department for 10 years.

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SR. NO.	QUESTION ANSWER
2.0	**VALIDATION MASTER PLAN (VMP)**
2.1	**What is VMP** Brief information about Qualification, Validation and calibration of Equipment, Instrument and System. A document providing information on the company's validation work programme. It should be define details of and timescales for the validation work to be performed. Responsibilities relating to the plan should be stated.
2.2	**Which Guideline follow for preparation of VMP** PIC/S (PI 006), WHO TRS 961, Eudralex Volume 4
2.3	**Contents of VMP.** • Cover Page, Table of contents • Approval of document • Introduction, Objective, Scope • Quality policy • Validation policy • Quality Risk Management Policy • Responsibility • Validation / Qualification Schematic Flow • Validation and Qualification approach • Revalidation and Requalification approach • Qualification Activity • Facility Qualification • Qualification and Validation of Utilities • Equipment Qualification • Laboratory Instruments and Equipment • Personnel Qualification • Products and Process Validation • Exhibit batches process validation • Cleaning Validation • Analytical Method Validation • Hold Time Study • Computerized System Validation • Vendor Qualification Program • Change Control, SOP, Training, Environment Monitoring, Preventive Maintenance / calibration • Terms and Definitions • List of Annexure • Revision History • References

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SR. NO.	QUESTION ANSWER
2.4	**Review Period** Any changes after approval of VMP shall be recorded in **Annexure-II** for keeping a track of changes taken place. VMP shall be revised at end of every calendar year, or as and when required through change control management system. Validation master plan is prepared at the initial stage of commissioning of a facility after the civil design, type, drawings are established. The VMP shall be prepared by QA, it should be reviewed by Department Head and approved by Plant Head and QA Head.
2.5	**Storage Period** Validation Master Plan shall be store by QA department for perpetual.
3.0	**QUALITY MANUAL (QM)**
3.1	**What is QM** The quality manual is a statement of the Company's Quality Policy and Quality Objectives of the organization.
3.2	**Which Guideline follow for preparation of QM** Eudralex Volume 4 (Chapter – 1 Pharmaceuticals Quality System), ICH Q8, Q9 and Q10, Schedule M.
3.3	**Contents of QM** • Introduction, Scope, Basics of Quality Management System • Quality Policy, Quality Objective Quality Risk Management Policy • Company Profile, Organization, Regulatory Basics • Documentation For The Quality Management System • Document Structure Production of Quality Management System • Accompanying Quality Management System • Design/Project Management, Qualification and Validation • Maintenance, Health requirements, Personnel hygiene requirements, including clothing • Complaints, Product Recall, Customer Management • Product Documentation, Labeling And Packaging Control • Product Quality Review, References
3.4	**Review Period** Every Two Years
3.5	**Storage Period** Perpetual

SR. NO.	QUESTION ANSWER
4.0	**CHANGE CONTROL**
4.1	**What is change control** A Process which ensures that changes to procedures, materials, methods, equipment, and software are properly documented, approved, validated and traceable. **CHANGE CONTROL PROCEDURE:** **DEFINATION:** **Change Control:** A formal system by which qualified representative of appropriate disciplines review proposed or actual changes that might affect the validated status of facility, systems, equipments or processes. **Temporary Change:** A change (departure from any established procedure/system/process) initiated for the evaluation of proposed procedure/system/process, which has been taken with prior approval to achieve the desired output, allowed for one time change and limited to a particular batch. For example change in batch size, manufacturing equipment, etc. **Permanent change:** A change initiated based upon scientific rational or historical GMP data or data generated through temporary changes. **Major Change:** Changes, proposed for improvements to process, materials, product and procedures which may have impact upon the identity, quality, purity, strength, stability, safety and efficacy or physical characteristic of the product. Notification to agency required. **Minor Change:** Changes, which does not have impact on the quality attributes like identity, quality, purity, strength, stability, safety, efficacy or physical characteristic of the product. **Changes are divided into two types:** 1) Permanent Change 2) Temporary Change The change control approval or rejection process shall require to be completed within 30 working days from the date of initiation of the change control. Change control preferably closed within 90 working days after Head –QA approval. If change control is not closed within specified timeline, initiator shall raise “Period Extension Request” as per SOP No. QAD 098. Initiating department Head shall review the extension request and write justification for delay with impact assessment. QA shall assess the impact of delay in action completion and approve / reject the Period extension request. Period extension shall be allowed for two times only. After this new change control shall be initiated. Change control trending shall be carried out monthly

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SR. NO.	QUESTION ANSWER

CLASSIFICATION OF TYPICAL CHANGES

Type of change	Critical	Major	Minor
Change in systems		√	
Change in manufacturing formula/process / New Products	√	√	
Change in expiry (related to stability)	√	√	
Change in critical Raw Material/solvent	√	√	
Change in specifications and test method	√	√	
Change in SOP for addition / deletion		√	√
Change in equipment		√	
Modification in critical equipment		√	
Modification / Up gradation in facility		√	
Change in stability program	√	√	
Change in key raw material source or supplier		√	
Change in storage conditions		√	
Change in primary packing material		√	
Change in secondary packing material			√
Change in packing style			√
Change in printed text on label		√	
Change in manufacturing location/site	√	√	
Change in manufacturing Batch Size	√	√	
Change in packing batch size			√
Change in control systems i.e. computers, Data Collection		√	
Formats and internal labels			√
Deletion of a product			√

Note: The list can be elaborated based on practical changes occurring at the locations.

Product Change **:** Change in key RM/Solvent, BOM, Process Parameters, In-process control, pack style, packing material, introduction of New Product etc

Engineering Change **:** Change in Facility design, equipment type, Maintenance parameters, utilities.

System Change **:** Change in software/firmware or its configuration etc.

Documentation Change: Change in SOP, STP, Document control procedures etc.

SR. NO.	QUESTION ANSWER

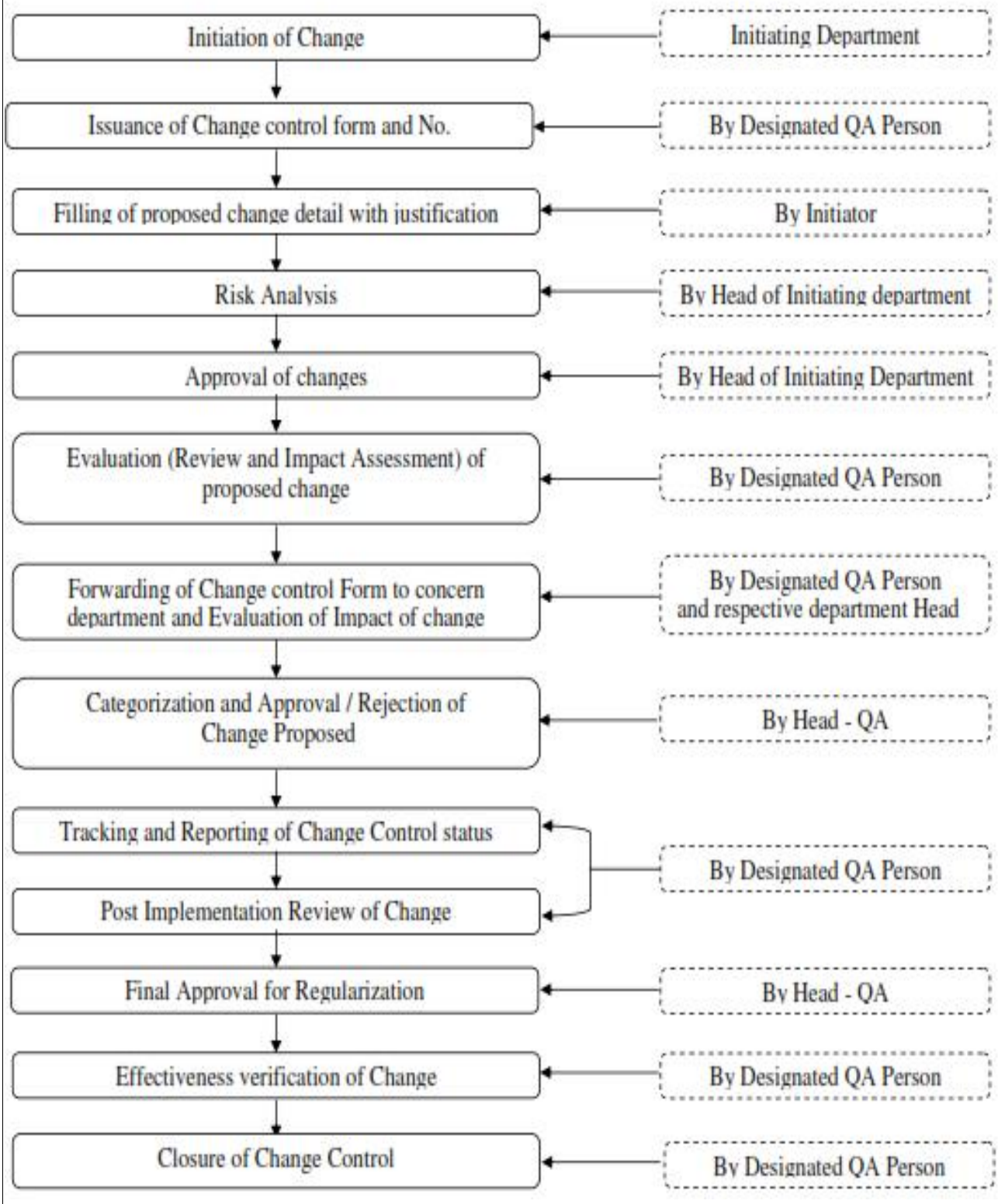
RECOMMENDED SUPPORTING STUDIES FOR CHANGE (S)

Type of change	Recommendations
Change in systems	Training, Change in relevant documents, and/or validation wherever required.
Change in manufacturing formula/process / New Products	Validation of three consecutive batches, with stability studies, method validation, specification, STP, Cleaning Validation verification in facility. Information and pre-approval from customer/regulatory authorities (as applicable)
Change in specifications	Stability studies on the changed specifications. Updating of SAP. Registration Dossier updation.
Change in test methods	Analytical Method validation, Updating of TDS, Registration Dossier updation.
Change in SOP for addition / deletion of instructions/formats/labels	Training, Change in relevant documents.
Change in expiry	Stability studies, Change in relevant documents, intimation to concerned departments. Registration Dossier updation.
Change/modification in equipment/ New equipment	Equipment qualification. SOP preparation, Training, Equipment list updation
Changes made for Marketing Authorization	Process related / system related.
Modification/Up gradation in facility	Facility qualifications, SMF update
Change in stability program	Stability studies in change conditions.
Change in critical raw material source	Vendor approval as per SOP
Change in storage conditions	Stability studies in changed conditions, Change in relevant documents/labels
Change in primary packaging material	Stability study, Change in relevant documents/BPR, Specification updation.
Change in pack style	Change in relevant documents/BPR, intimation to concerned departments.
Change in printed text	Change in relevant documents/BPR. Intimation to concerned departments.
Change in manufacturing batch size, manufacturing site/location	Partial validation of three consecutive batches, accelerated/long term stability studies depending on the change.
Change in control systems i.e. computers, configuration of software/firmware, etc.	Validation of the new control system.

Note: This list is not exhaustive and can be extended based on practical changes occurring at the locations.

SR. NO.	QUESTION ANSWER

FLOW DIAGRAM FOR THE MOVMENT OF CHANGE CONTROL



PHARMA BOOK

SR. NO.	QUESTION ANSWER
5.0	**DEVIATION**
	DEFINATION: **DEVIATION:** Deviation is an unexpected event that occurs during the on-going operation / Activity / Documentation / Entries at any stage of Receipt, Storage and Manufacturing, Analysis and Distribution of Drug Products / Intermediates / Raw Materials / Packing materials. Deviations are to be reported as and when they occur and to be investigated for impact assessment. **Critical Deviation:** Deviation that could have significant impact on the product quality or GMP system. Examples of critical deviations are given below but not limited to: • Cross contamination or product mix up in a product. • Failure to process step during manufacturing. • Use of obsolete batch document / test method. • Filter integrity failure. **Major Deviations:** Deviation that could have a moderate to considerable impact on the product quality or GMP system. Examples of major deviations are given below but not limited to: • Machine breakdown during processing • Mix ups of cartons of same product with different strength.
5.1	**Minor Deviations:** Deviation unlikely to have a detectable impact on product quality or GMP system. Examples of minor deviations are given below but not limited to: • Minor errors in batch records or document that not affecting the integrity of data. • Spillage of material during dispensing. • Failure to meet environmental condition during batch processing. **PROCEDURE:** All deviation shall be documented, investigated, tracked and trended. All deviation shall be reported as when they occur. The person who observes the deviation shall inform the immediate supervisor or concern department head/designee and to Quality Assurance. As per the severity of deviation and stage of process, the process may be stopped for initial assessment. QA shall issue the “Deviation Control Form “on the request of initiator (Concerned department) by assigning deviation number The initiator shall fill the details (like Product / Material / Equipment / Document / Other If any and Batch No. / A.R.No. If applicable) in deviation control form.

Simpal Baria

SR. NO.	QUESTION ANSWER
	Initiator shall do the initial assessment and shall take suitable immediate action according to the nature of deviation and inform to department head and concern QA person. Initial impact assessment shall be done by the observing department head / designee and designated person QA. Recommendation for continuation of process / discontinue the process shall be given by head of department and Head QA or designee. Based on nature of deviation, initial assessment and immediate action taken, Head of initiating department shall approve the deviation for further evaluation of QA. After approval of deviation from head of initiating department deviation form shall be forwarded to QA for evaluation. During evaluation, designated QA person shall verify whether the deviation is quality relevance or not and whether deviation is a repeat occurrence or not. If it is quality relevance, impact shall be assessed on other areas/departments. And if it is a repeat occurrence, impact assessment shall extend to verify the effectiveness of previous CAPA taken. After evaluation categorizes deviation into critical, major or minor based on the evaluation of impacted areas and product quality impact. If deviation is categorized as Critical or Major, Cross Functional Team comprising of technical experts from different department (as per the nature of deviation) shall be form to investigate the root cause of deviation. If deviation is minor, investigation shall be carried out jointly by designated QA person along with a person from department where deviation happened. Failure Investigation and Root Cause identifications shall be carried out by the investigation team using investigational methodologies. Upon identification of root cause of failure, the probable root cause of failure shall be documented. Corrective actions and preventive actions shall be recommended to prevent the reoccurrence of the same. The deviation including investigation report (wherever applicable) shall be closed within 30 working days of the initiation date. The initiation date is the date of observation of deviation. If deviation is not closed within specified timeline, initiator shall raise “Period Extension Request” as per SOP No. QAD 098. Initiating department Head shall review the extension request and write justification for delay with impact assessment. QA shall assess the impact of delay in action completion and approve / reject the Period extension request. Deviations shall be closed only when all relevant actions in the CAPA log are completed.

SR. NO.	QUESTION ANSWER

Continuous trending of deviations shall be carried out on monthly basis

QA shall carry out trend analysis for all the deviation in the whole year at the beginning of the next year by using monthly trend data. A copy of trend analysis shall be forwarded to Head CQA.

The record retention for all closed deviation and investigation reports shall be not less than 7 years or as otherwise agreed with concerned regulatory body.
All deviation and investigation reports shall be kept in custody of QA and QA shall maintain the Deviation register.

Example of Deviation:

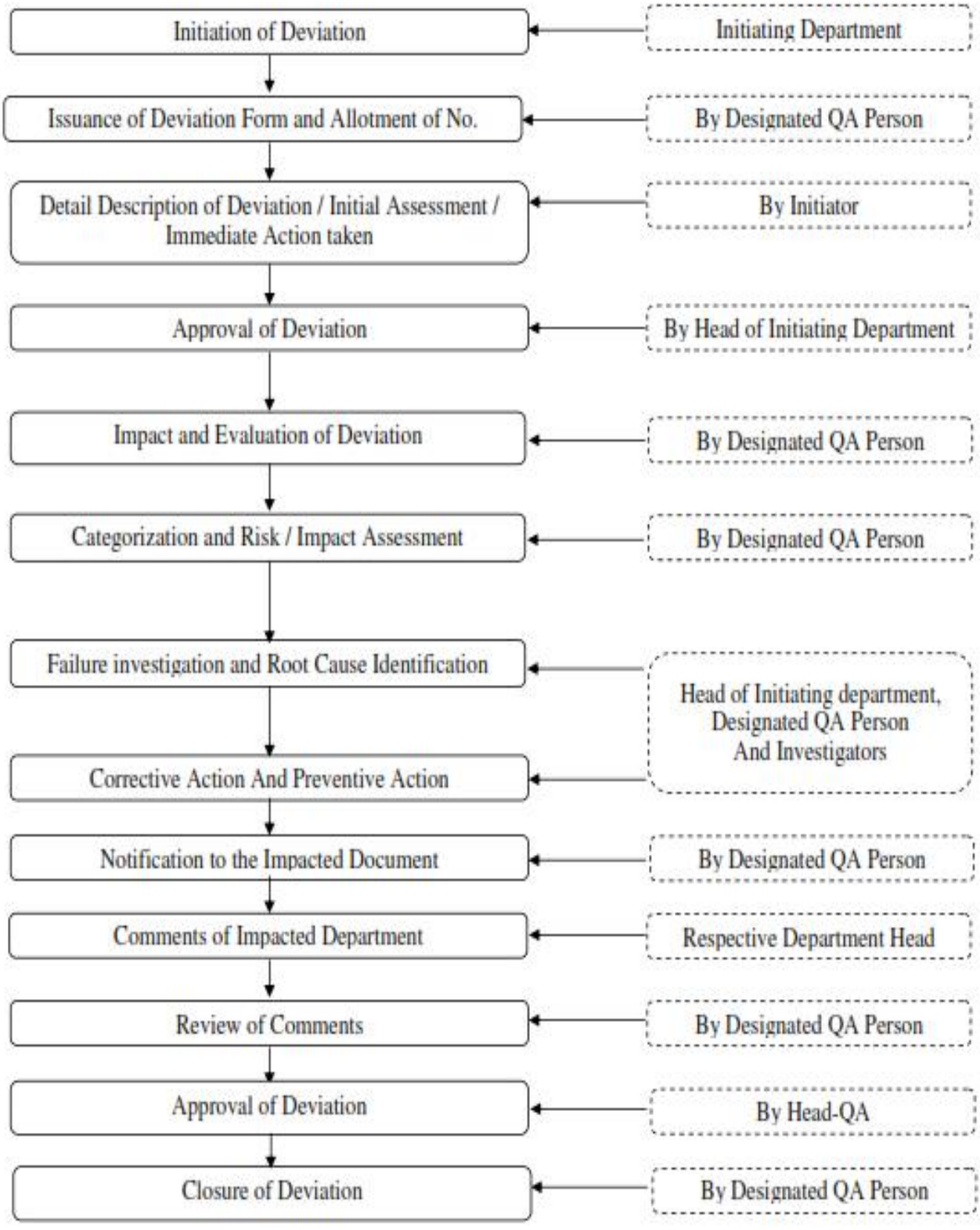
Activity / Document	Examples of Deviations
Documents	Wrong version, data missing or incorrect data.
Procedures (SOPs)	Procedure not followed.
Batch records (BMR / BPR)	Steps not followed, Steps skipped.
Incoming Materials requiring QA release	Deviations reported by receiving department including damaged or incorrect shipment, missing or questionable label or documentation
Sampling of incoming materials	Damaged or incorrect shipment, incomplete or incorrect documentation
Material and their status	Incorrect or unapproved material used, questionable release
Batch Yield	Established yield or reconciliation is not met
Process Control Parameters	Parameters not in control and / or not followed.
Sampling	Improper sampling technique or frequency, Sample identity mix- up
Material Holding time and holding conditions	Holding time or conditions not met, incorrect vessel used.
Environmental controls	Parameters exceed limits
Calibration	Equipment/ instrument out of calibration or tolerance, log or sticker missing
Equipment function / Facility issues	Equipment/ instrument failure, incorrect equipment/ area used
Quality	Failures errors reprocessing, reinsertion

SR. NO.	QUESTION ANSWER

Activity / Document	Examples of Deviations
Data entries	Calculation error, missing of critical reading
Signatures / Approvals	Inconsistent dates / initials, in appropriate approvals
Equipment / Area cleaning, Line clearance, sterilization and Sanitation	Inappropriate cleaning, Line clearance failure, questionable house-keeping.
Validation / Qualification related deviation	Failure to meet validation/ qualification requirements, non-validated equipment, unapproved protocol
Testing	Testing not performed within established timeframe, testing not performed
Product Identification Discrepancy	1) No pallet identification number on pallet. 2) Case/carton/Label/Product/Lot not identified, Status is incomplete or incorrect. 3) A lot number discrepancy either physical or systemic between what is expected and what is received.
Mixed Lots on Pallet	More than one lot on a single pallet without proper placard and separation.
Potential Product Defect	1) Potential product has a deviation other than Packaging and labelling 2) Temperature Deviation – Temperature goes outside the specified range
Third Party / Vendor or Supplier issues	1) Incorrect / defective packaging supply- Supplies that do not meet specification. 2) Third Party Vendor Error – An error by third party vendor that effects product identity, safety, stability 3) Transportation error – An error made by a carrier of our products.
Lot Status Issues	1) Lot status discrepancy – The status of a lot is not the same in all computer systems. A situation where the true lots status in question. 2) Improperly Placard – Placards do not reflect actual product status
Mechanical Failure	A Mechanical deviation within the unit that results in a possible GMP deviation.

SR. NO.	QUESTION ANSWER

FLOW CHART FOR DEVIATION HANDLING



SR. NO.	QUESTION ANSWER
6.0	**MARKET COMPLAINT**
6.1	**DEFINATION:** **MARKET COMPLAINTS** A complaint is any expression of dissatisfaction with a product or service marketed. Any written/ genuine verbal communication received directly from any customer, retailer, distributor, healthcare professional, regulatory agency, patient (Consumer) or field staff, regarding the safety, identity, strength, purity, efficacy, quality, shortages or any other such complaints shall be considered as a Market Complaint. **PROCEDURE:** All the market complaints shall be received by marketing department (Domestic/International) at Head Office. Concern marketing person shall record all the details of complaint product, name and address of complainant and nature of complaint in "Market Complaint Form and forward the same to Head-CQA. Head-CQA/Designee shall ensure that all information available in the "Market Complaint Form" concerning the particular complaint. Ensure that all required information is entered and all required information for complaint investigation is received and if not, then Head-CQA shall ask to send required information to marketing department. In case of quality/efficacy related complaint, Head-CQA/Designee shall request the complainant/marketing department for complaint sample. Head-CQA/Designee shall follow up for complaint sample up to 15 days from the date of complaint. If marketing department is unable to provide the required information (Details of complaint) and complaint sample to Head-CQA then the same complaint shall treated as non-justified complaint and closed. If the required information provided by marketing department/complainant, Head - CQA shall acknowledge the “Market Complaint Form” by signing on received by column with date and the same shall be forwarded to Head-QA/Designee at site. Head-QA/Designee shall enter the complaint details in market complaint log After logging of complaint, Head-QA/Designee shall start the investigation of compliant based on guideline provided

SR. NO.	QUESTION ANSWER

Sr. No.	Example of Complaint	Suggested investigation
1.	Ineffectiveness / Poor Quality / Inadequate response of the drug product.	• History of the product. • Physical inspection of complaint & control sample. • Review of batch document for, o API calculation. o Qty. added of API & excipients (dispensing slip/raw material requisition against bill of material. o Source of material. o Dispensing precautions: e.g. API dispensing & storage in the dedicated polybag or container etc. o Processing precautions, low light, and nitrogen flushing or any other. o Processing parameters. o In process checks by production & QA. o Any deviation, which has direct or indirect impact on product quality. • In process quality control data. • Review of FP analytical report & trend. • Review of stability data. • Complaint & control sample analysis for, o Weight variation, Hardness & friability. o Content uniformity. o Dissolution. o Assay. o Degradation. o Moisture content. o Biological assay. o Storage condition. • Audit of distributors, C & F agent or retailer etc.

SR. NO.	QUESTION ANSWER

Sr. No.	Example of Complaint	Suggested investigation
2.	Less content in capsules/ tablet	• Physical inspection of complaint & control sample, For, o Minor crack. o Improper sealing. o Condition of container label & / or carton to eliminate possibility of leakage. • Review of batch manufacturing record for, o API calculation. o Qty. added of API & excipients (dispensing slip/raw material requisition against bill of material. o In process checks by production & QA. o Yield & reconciliation of the batch. • In process & FP quality control data. • Equipment usage logbooks of compression or capsule filing machine for breakdown. • Complaint & control sample analysis for, o Average weight o Dissolution. o Content uniformity. o Assay. o Degradation. o Weight variation.
3.	Bulging of strip/blister pockets.	• History of the product. • Physical inspection of control & complaint sample. • Review of storage condition. • Review of stability data. • Analysis of complaint &/or control sample for, o Assay. o Degradation.
4.	Presence of foreign matter (Living / non living).	• History of the product. • Physical inspection of complaint & control sample. • Physical inspection of particular AR No. of RM used for manufacturing of the batch. • Review of batch manufacturing record. • Cleaning record of mfg equipments & area. • Environmental monitoring data. • Analysis of complaint sample for, o Assay, Degradation. o Microbial contamination test. • Training record of visual inspectors.

SR. NO.	QUESTION ANSWER

Sr. No.	Example of Complaint	Suggested investigation
5.	Adverse reactions (e.g. vomiting, severe cramps, rashes etc)	• Review of complaint history. • Review history of the patient. • Review of package insert. • Microbiological analysis of complaint sample. • Pharmacology of the API & related formulations.
6.	Discoloration of tablets /capsules.	• History of the product. • Physical inspection of complaint & control sample • Review of batch manufacturing record for, o Special precautions required during processing e.g. controlled humidity/ light sensitive & temperature etc. o Cleaning record of granulation, compression and coating equipments & area. o In process checks by production & QA during manufacturing & packing. • Analysis of control & / or complaint sample for, o Assay, Degradation, Stability data • Storage condition.
7.	Damaged / broken / leakage in capsule	• Physical inspection of complaint & control sample. • Review of batch manufacturing record for, o Visual inspection record o Temp. & humidity conditions o Capsule filling machine setting parameters o In process checks during manufacturing & packing by QA & production. • Vendor of EHG capsule. • Equipment logbook of capsule filling machine for breakdown. • Training of the visual checkers. • Compatibility study of empty hard gelatine capsule with excipients.
8.	Broken tab.	• History of the product. • Physical inspection of complaint & control sample. • Review of batch manufacturing record for, o In process checks by production & QA during manufacturing & packing. o Visual inspection record. • Review of trend of processing, in process & FP Parameters and Handling of the bulk product. • Training record of the visual checkers & strip/blisters

SR. NO.	QUESTION ANSWER

Sr. No.	Example of Complaint	Suggested investigation
9.	Product or batch mix up.	• Physical inspection of control & complaint sample for physical appearance of primary pkg. material of two products under question. • Review of system followed to ensure proper segregation product at different stages. • Review of logbooks of machine at every stage to know the previous or next product taken on the same machine & precautions taken to ensure absence of same /similar product in the surrounding area. • Review of other products packed on the same day on the nearby labelling machine or packing line of product under question. • Review of batch manufacturing record for, o Machine & line clearance record at different stages. o Reconciliation of packaging materials. o Reconciliation of bulk & FP. • Analysis of control &/or complaint sample for, o Identification test of two products under question. o Identification test of preservative. • Wrong labelling/ packing. • Training record of checker and packers.
10.	Poor quality of cap	• History of the production • Physical inspection of control & / or complaint sample. • Vendor of packing (cap) material. • Compatibility study • Review of stability data.
11.	Faulty product (Product Counterfeiting)	• History of the product. • Comparison of complaint sample with control sample for appearance of strip/ label (font size of letters, printed text matter, size of the pocket, gap between the two pockets, knurling pattern, logo of the company, movement of tab or cap in the pocket etc). • Comparison of complaint sample with control sample for appearance of tablet or capsule (size or dimensions, colour, imprint, embossing, edge type etc). • Analysis of complaint & / or control sample.

SR. NO.	QUESTION ANSWER

Sr. No.	Example of Complaint	Suggested investigation
12.	Empty primary container (Bottle / pocket of strip or blister)	• Physical inspection of control &/or complaint sample. • Logbooks of striping or blistering machine for breakdown. • Working of Non Fill Detector (NFD) or Blister Inspection system (BIS) • Review of batch document for, o In process checks by production & QA during filling. o Leak test record. o Visual inspection record. o In process checks by production & QA during packing (e.g. on line compressed air flow or any other system followed to remove empty plastic container or empty pocket in strip or blister). o Yield & reconciliation of the batch & comparison with trend. • Balance or checkweigher performance & calibration check record. • Weight variation record of packed cartons &/or shippers. • Proper segregation of packed & empty boxes. • Training record of the visual inspectors.
13.	Receipt of product in different carton/ having different label.	• Complaint sample observation. • Physical inspection of control sample. • Previous & next product packed on the same machine. • Appearance of packing material of two products under question. • Review of batch document for, o Line clearance (by packing & QA) record. o Reconciliation of packing material. o Machine & line clearance record. o In process checks by packing & QA. • Storage of packing material in the store & in pkg. Dept. • Procedure to be followed for the left over pkg. Material after completion of packing. • Inspection of remaining stock of PM of the products under question. • Training of checker and packers.

SR. NO.	QUESTION ANSWER
	Head-QA/Designee shall write the complaint product details and categorize the complaint as Critical/Major/Minor in "Market Complaint Investigation Form **Critical Complaint:** A complaint that strongly indicates the purity, identity, safety or efficacy of a product may have been compromised and has the potential to cause a life threatening or serious health situation. **Major Complaint:** A complaint that indicates the purity, identity, safety or efficacy of a product may have been compromised, but does not present as a life threatening or serious health risk. **Minor Complaint:** A complaint that is neither critical nor serious If complaint is categorized as critical, Head-QA shall intimate (within 24 hours from the receipt of the complaint) to Head - Marketing/Distribution for the immediately stoppage of the further sale and distribution of the batch till the completion of investigation Head-CQA / QA shall communicate to FDA / Regulatory Affairs / Customer / MA holder / QP / Customer regarding market complaint based on nature of market complaint The investigation shall be carried out by a team of representatives from QC, QA, Production, Engineering, R&D, ADL, Marketing, RA and etc. (as per nature of complaint). The investigation shall involve, but not restricted to, examining reserve samples, complaint samples and other samples, review of batches of complaint product, review of batch documents and other related logbooks and documents etc. If complaint sample is received along with the market complaint, it should be thoroughly examined for the integrity of the pack, physical appearance and evidence of deterioration if any. Complaint sample needs to be checked for detection of counterfeiting. Check for counterfeit sample shall be carried out in accordance with title outline in this SOP as “Handling of Counterfeit Samples”. In case of quality testing related complaint, QA shall send the complaint sample (if available) or reserve sample of the complaint batch to quality control department for analysis. Depending on the nature of complaint, the reserve sample and complaint sample is to be analyzed for the relevant test parameters specified by Head-QA. Analysis of the sample is to be carried out as per the specification by which the product was registered. After completion of analysis, QC shall send the analytical report to QA for further investigation. The Head-QA/Designee shall review the analytical report for compliance to specification that may be relevant to the complaint. If the results of reserve samples and complaint samples are complying with the specification or either of samples complying with specification, probable root cause shall be identified with the help of guideline mentioned in **Annexure - VI**.

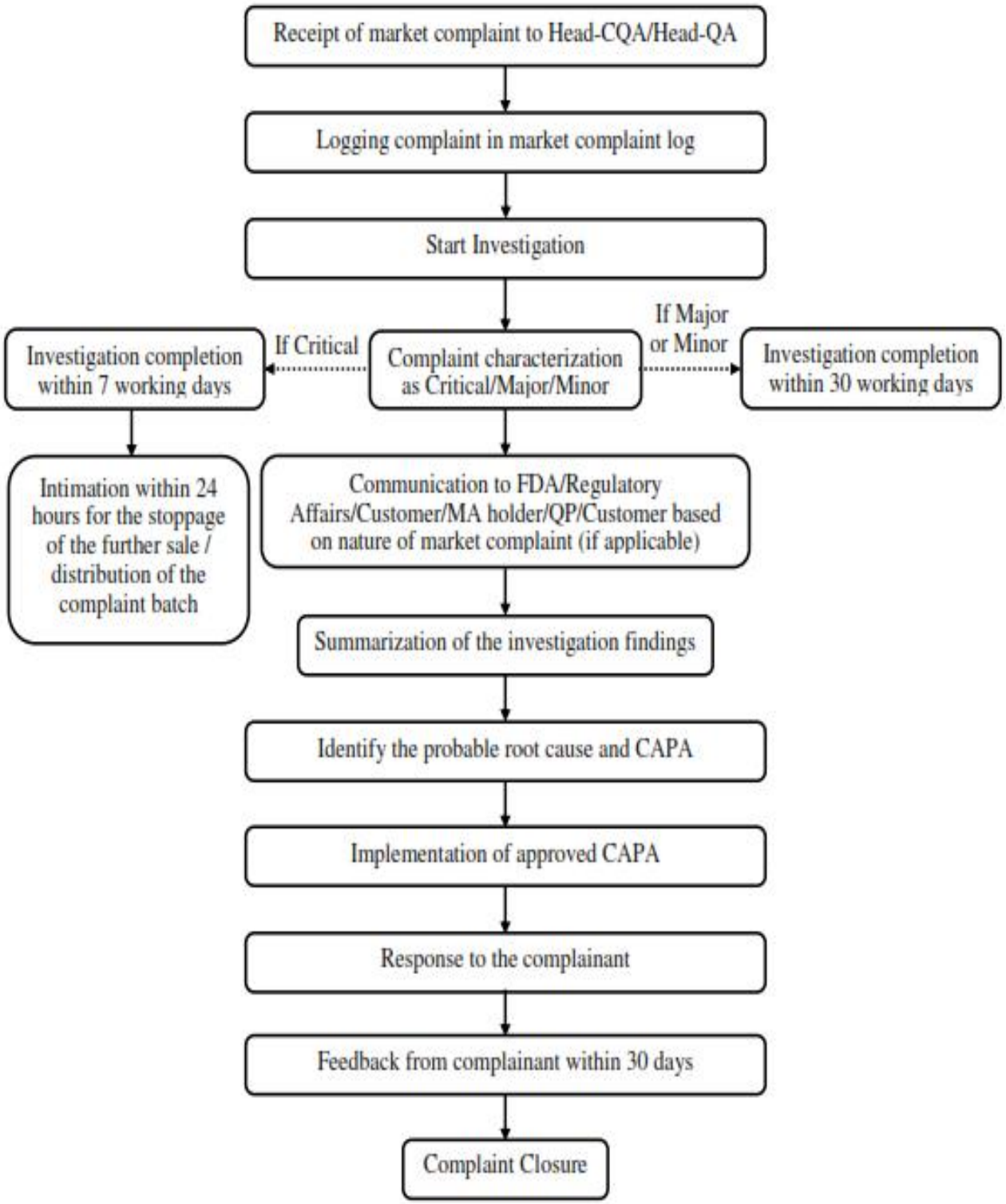
SR. NO.	QUESTION ANSWER
	If any OOS observed in the control samples, then investigate as per "OOS" SOP No. QCG 034. QA shall ensure the storage of remaining complaint sample in secured manner under desired storage conditions till the closure of complaint. Complaint samples received shall be destroyed during of closure of complaint. Head - QA shall decide for the extension of the investigation if similar complaints for the product or other products have been received. Head - QA shall form an Investigation team, comprising of technical persons from requisite departments such as QA, QC, Production, Stores, Engineering, R&D, ADL, RA and Marketing depending upon the nature of complaint. Investigation team shall investigate the complaint to identify the root cause and to take necessary CAPA. For investigation methodology/tools SOP No. QAD 092 “Failure Investigation and Root Cause Analysis” and for CAPA SOP No. QAD 042 “Corrective and Preventive Action” can be followed. In addition, guidelines as mentioned in **Annexure-VI** shall be followed. The complaint investigation may include the concerned Analytical Report, Batch Manufacturing Record, Batch Packing Record, instruments/equipments logbooks, Training Records, Stability Records, Cleaning Records, Calibration records, Environmental Monitoring Records of various stages of processing, Storage, Dispatch and distribution of the batch and other related documents such as any deviation in concerned batch. Previous and next batches of the product shall also be investigated in case of same raw materials / packing materials are used for the batch. The investigation shall extend to other batches of the same drug product and other drug products if investigation shows the possibility of similar defects in other batches/products. If required, observations of stability study samples and review of data to be carried out. If required, help of R&D - Formulations shall be taken in case of process related problems. Take Medical department opinion (if any) from medical experts as a part of investigation for clinical related complaint. Investigation team shall identify the root cause of complaint based on the observations made during investigation. Manager-QA shall summaries the findings in the “Market Complaint Investigation Form” and the same shall be forwarded to Head-QA for impact assessment as per root cause identified.

SR. NO.	QUESTION ANSWER
	Head-QA and other members of investigation team shall suggest corrective and preventive actions against the identified root cause and investigation report shall forward to Head-Manufacturing. Head-Manufacturing shall review and recommend suggested corrective and preventive actions. Finally Head-QA shall review and approve the investigation report and CAPA. In case the investigation reveals nature of complaint as Critical, Head-QA shall initiate recall of the complaint batches which exist in the market as per SOP No. QAD 009 of "Product Recall". Head-QA/Designee shall send the investigation report to all concerned persons with the corrective and preventive actions in detail along with target completion date of actions. **TIME LINES FOR INVESTIGATION:** Investigation shall be completed within 7 working days for critical complaint and 30 working days for Major/Minor (or as per Technical Agreement requirement or Regulatory Agency requirement where appropriate) and same shall be sent to marketing department immediately after investigation. If the complaint is from regulatory agency / MA holder, investigation shall be completed according to their timelines. Approved Market Complaint Investigation report shall be forwarded to Marketing department, who in turn send response to the complainant. In case of complaints from export market, QA/RA shall check the regulatory impact. While reviewing the impact, QA/RA shall consider the specific requirements mentioned in Technical Agreement as well as country specific requirements. Wherever applicable, the regulatory agency / MA Holder / QP shall be informed if action is being considered following possible faulty manufacturing, product deterioration, detection of counterfeiting, or any other serious quality problems with a product that could result in a recall or abnormal restriction on supply. The corrective and preventive actions for all the complaints shall be tracked as per the SOP No. QAD 042 "Corrective and Preventive actions". The acknowledgement from the complainant for the receipt of the response shall be obtained against the "Letter of Acknowledgment" as per **Annexure-VIII**. If complainant provides acknowledgment through email / letter / fax, same shall be documented. The complaint shall be treated as "Closed" after receiving feedback from the MAH/Customer/Complainant. The time period for receiving feedback from the customer is 30 days. If no further query is received within the stipulated time, the complaint shall be treated as closed. The closure details shall be recorded in "Market Complaint Closure Form" as per **Annexure-IV**.

SR. NO.	QUESTION ANSWER
	Implementation of suggested corrective and preventive actions shall be verified by Head-QA/Designee. Designated QA person shall ensure that all correspondence related to complaint is available at site before closure of complaint. Correspondence if made by the Marketing department / Medical department shall also be requested from the respective department. In case of receipt of any complaints through a legal route, the investigation findings shall be communicated by Medley legal department in consultation with Head – Quality / QA. A copy of the response shall be kept with the complaint record at QA Daman. **Handling of Counterfeit Samples:** In case if the received complaint samples is suspected to be counterfeit, then it shall be examined as follows: → In Comparison of packaging / labeling of the complaint sample with reserve sample. → Check the coding style / printing of the batch details. → Quality of the packaging components. → Organoleptic properties of the drug in comparison with reserve sample. If the comparison of the packaging components, coding style and organoleptic examination does not reveal the conclusive evidence then perform the analysis of the complaint sample along with reserve samples. During the course of investigation, if the complaint sample received found to be counterfeit then Head-QA shall inform to marketing and Medley representative in countries where the company's products are marketed for appropriate action through Head-CQA. In case of counterfeit complaint, put relevant remark in “Market Complaint Log” and in “Market Complaint Investigation Form” and close the complaint. **REVIEW AND TRENDING OF COMPLAINTS:** Head - QA shall review the complaint status every quarter to evaluate specific or recurring problems which require further attention. Designated QA person shall prepare complaint yearly trends. Trends shall be reviewed by Head-QA and required action shall be taken accordingly. The records of all market complaints for drug products and the follow-up / related records shall be kept for one year from the date of expiry of the batch for which the complaint has been received.

SR. NO.	QUESTION ANSWER

FLOW CHART OF MARKET COMPLAINT INVESTIGATION

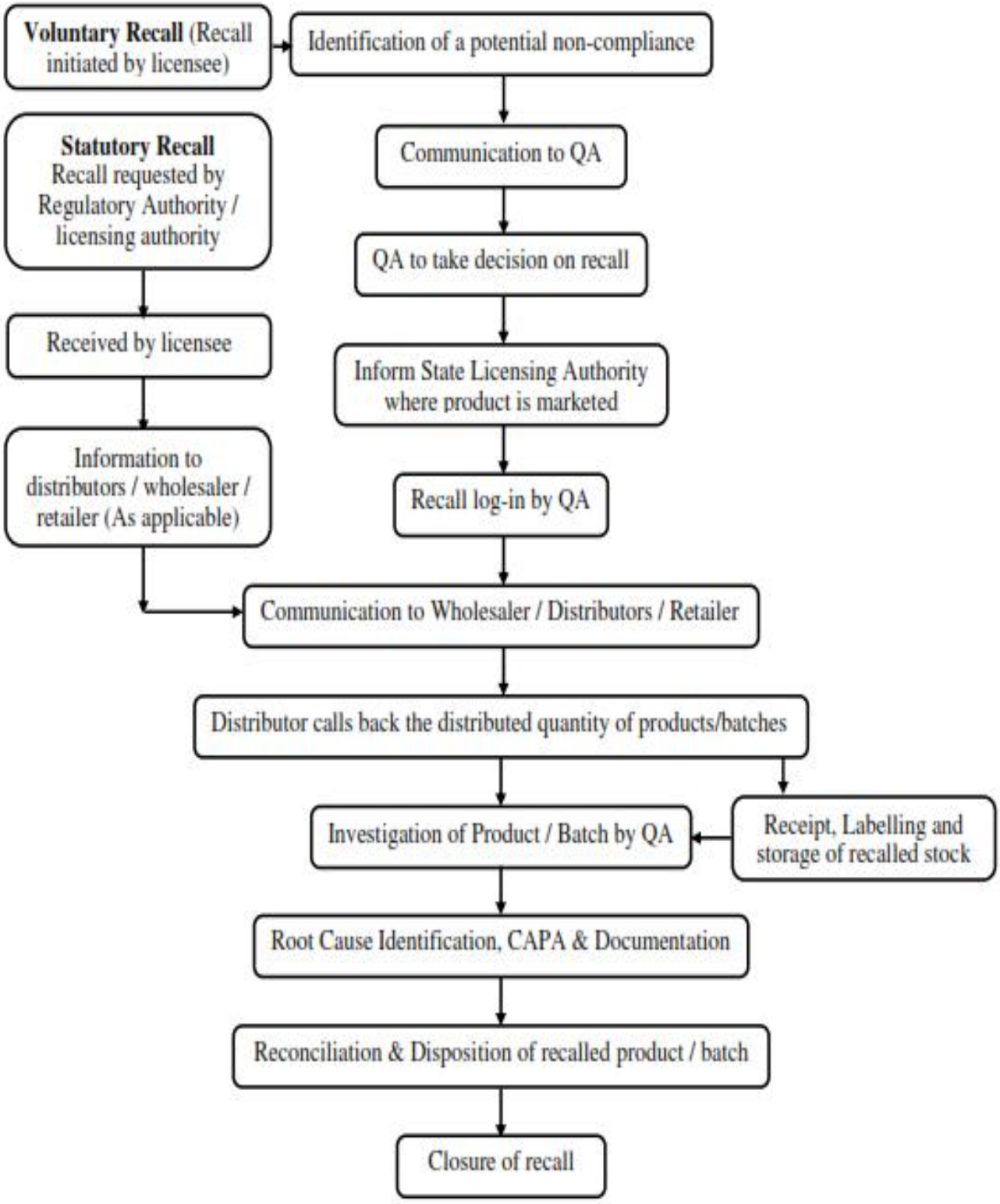


SR. NO.	QUESTION ANSWER
7.0	**PRODUCT RECALL**
7.1	**DEFINATION:** **PRODUCT RECALL:** Removal or correction of marketed products for the reasons relating to deficiencies in quality, safety or efficacy, including labeling considered to be in violation of the laws. **PROCEDURE:** Any batch of a product not meeting the defined quality standards has to be recalled from the market. Recall can be of two types; Voluntary Recall and Statutory Recall. **Voluntary Recall:** Voluntary recall can be triggered by any incident that affects the quality, safety and efficacy of the batch/product in question such as • If the batch or batches are found to be not complying with the regulatory specifications during the post marketing stability study • If the batch is found to be defective during investigation of market complaint. • During any failure investigation, if it is observed that the failure under investigation might have adverse quality impact on already released batch. • If any unusual observation is noted during visual inspection of reserve samples which indicate an impact on quality of the product after investigation. • If the post marketing surveillance reports /pharmacovigilance reports indicates that there is serious safety risk associated with the product. **Statutory Recall:** Statutory recall can be triggered in response to the direction or mandate by the Drug Regulatory Authorities. • To recall the drug product/batch, considered to be in violation of the laws, it administers such as not of standard quality etc. • To recall the banned drugs. • Labeling and / or Promotional materials that are considered to be in violation of law. Recall Logging: Once a potential product recall situation is identified Head-QA/designee shall enter the details in Product Recall log Designated QA person shall assign a product recall number to the same

SR. NO.	QUESTION ANSWER
	In case of product recall, Head-QA or his designee shall intimate to the members of Recall Co-ordination Committee (RCC) and organize for a meeting. The RCC members shall evaluate the known information on the nature and extent of the health risk taking inputs from Head-Medical department Based on the evaluation, the RCC members shall classify the recall as Class I, Class II and Class III to indicate the relative degree of health hazard of the product being recalled or considered for recall. **Class I Recall:** These are recalls which result from quality defects of medicinal products which are potentially life threatening or could cause serious risk to health. **Class II Recall:** These are recalls due to quality defects which may cause mistreatment or harm to the patient but it is not life threatening or serious. **Class III Recall:** These are recalls due to quality defects which are unlikely to cause harm to the patient, and the pose a significant hazard to health but where a recall has been initiated for other reasons, such as non-compliance with the marketing authorization or specification. **Levels of Recall:** The level (or depth) of recall of a product/batch shall be determined based on recall classification and level to which distribution has been taken place. There are three levels of recall such as consumer /user, retail and wholesale. **Consumer or User Level:** This may vary with product, including any intermediate wholesale or retail level. Consumer or user may include individual consumers, patients, physicians and hospitals. **Retail Level:** Recall to the level immediately preceding consumer or user level. It includes retail shops, pharmacies, hospital pharmacies, dispensing physician, institutions such as clinics and nursing homes, etc. **Wholesale Level:** All distribution levels between the manufacturer and retailer. **Class I Recall:** Notification and acknowledgement of receipt of recall notification within 24hrs. **Class II Recalls:** Notification and acknowledgement of receipt of recall notification within 48 hours. **Class III Recalls:** Notification and acknowledgement of receipt of recall notification within 5 days. Mock recall shall be done to evaluate the effectiveness of arrangements periodically to recall the products from EU / US / Australia / other export markets and domestic markets. Mock recall is applicable only to markets where product is already marketed. Frequency of Mock Recall shall be once in two years or as per MA Holder / Contract giver requirement.

SR. NO.	QUESTION ANSWER

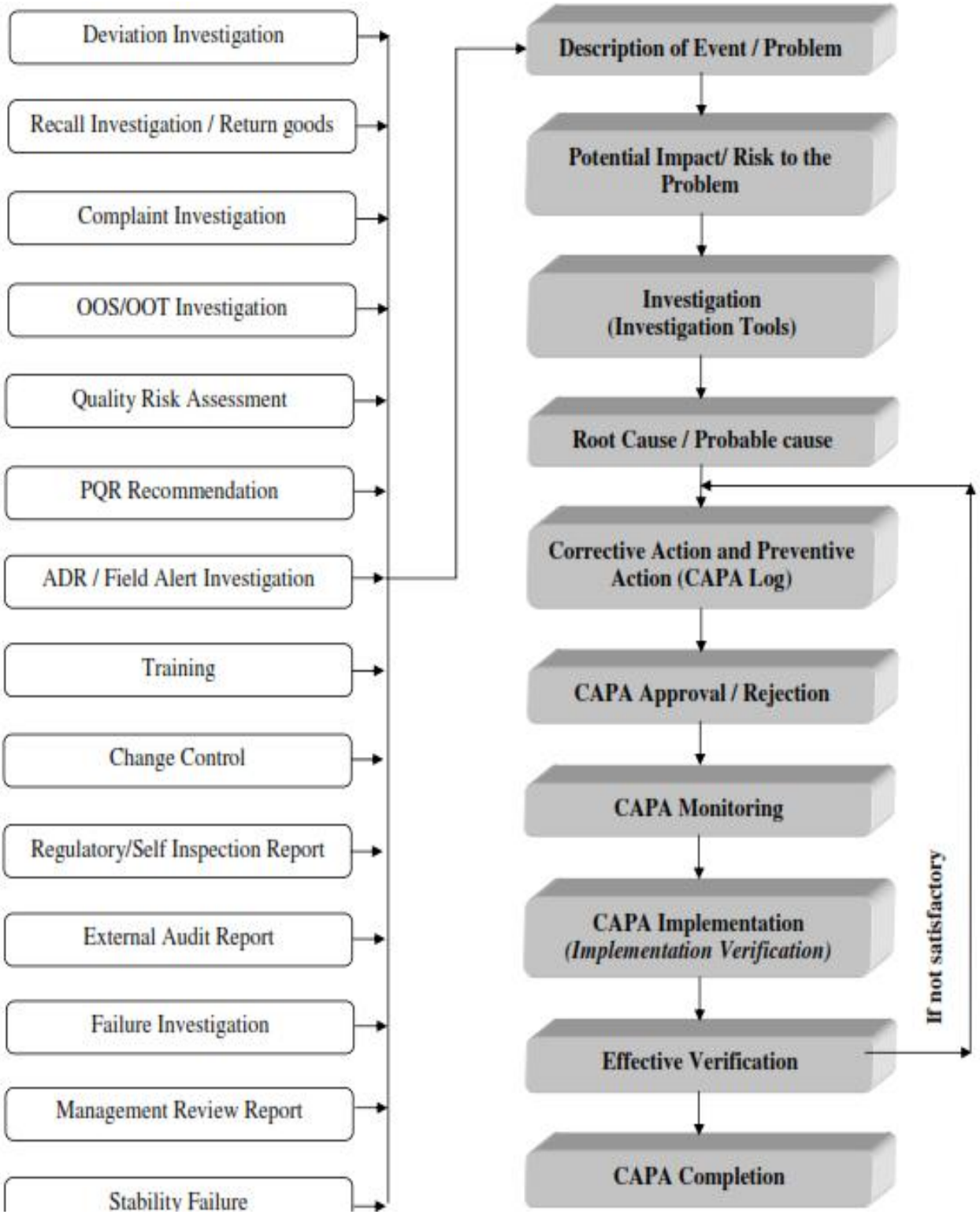
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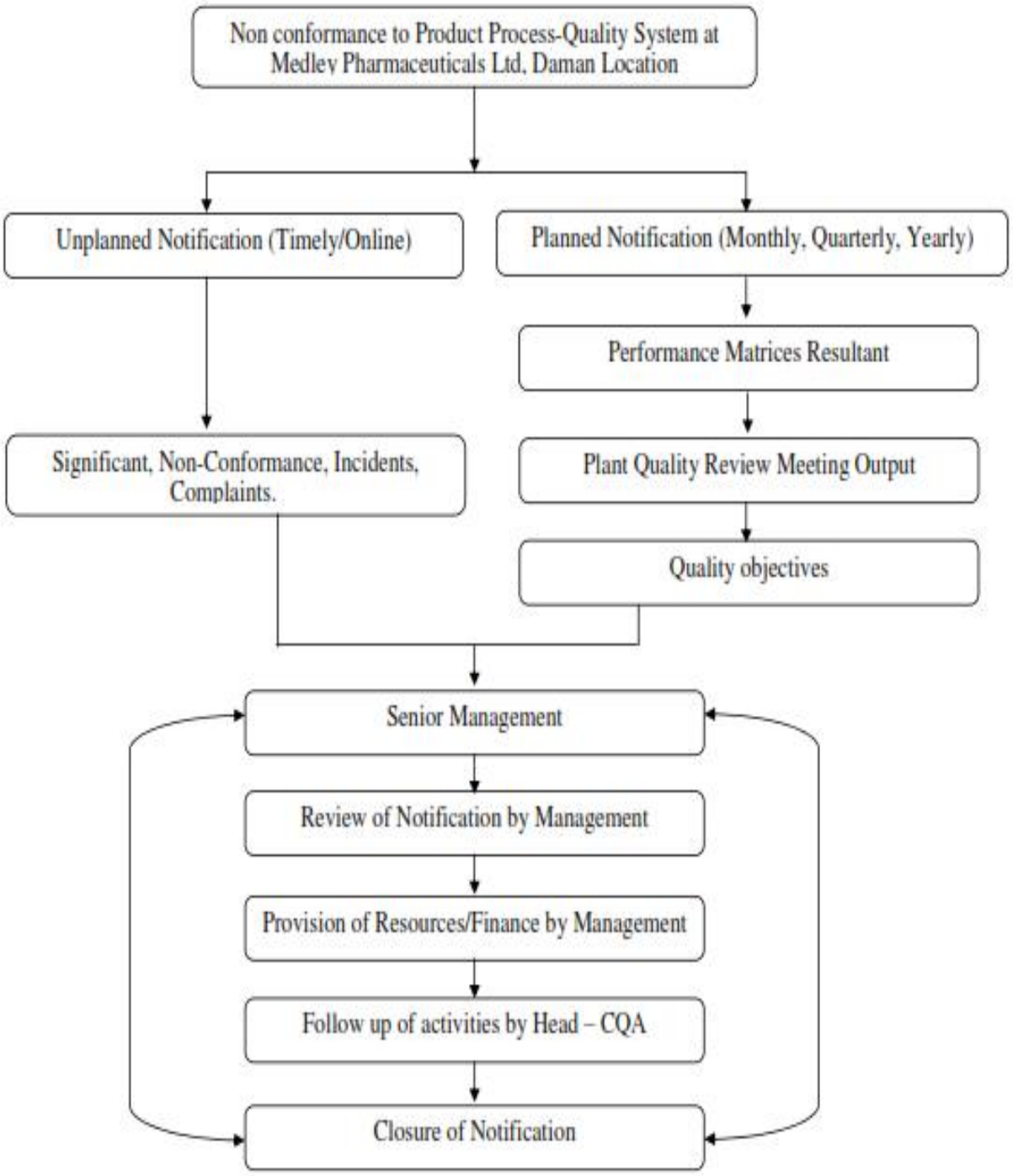


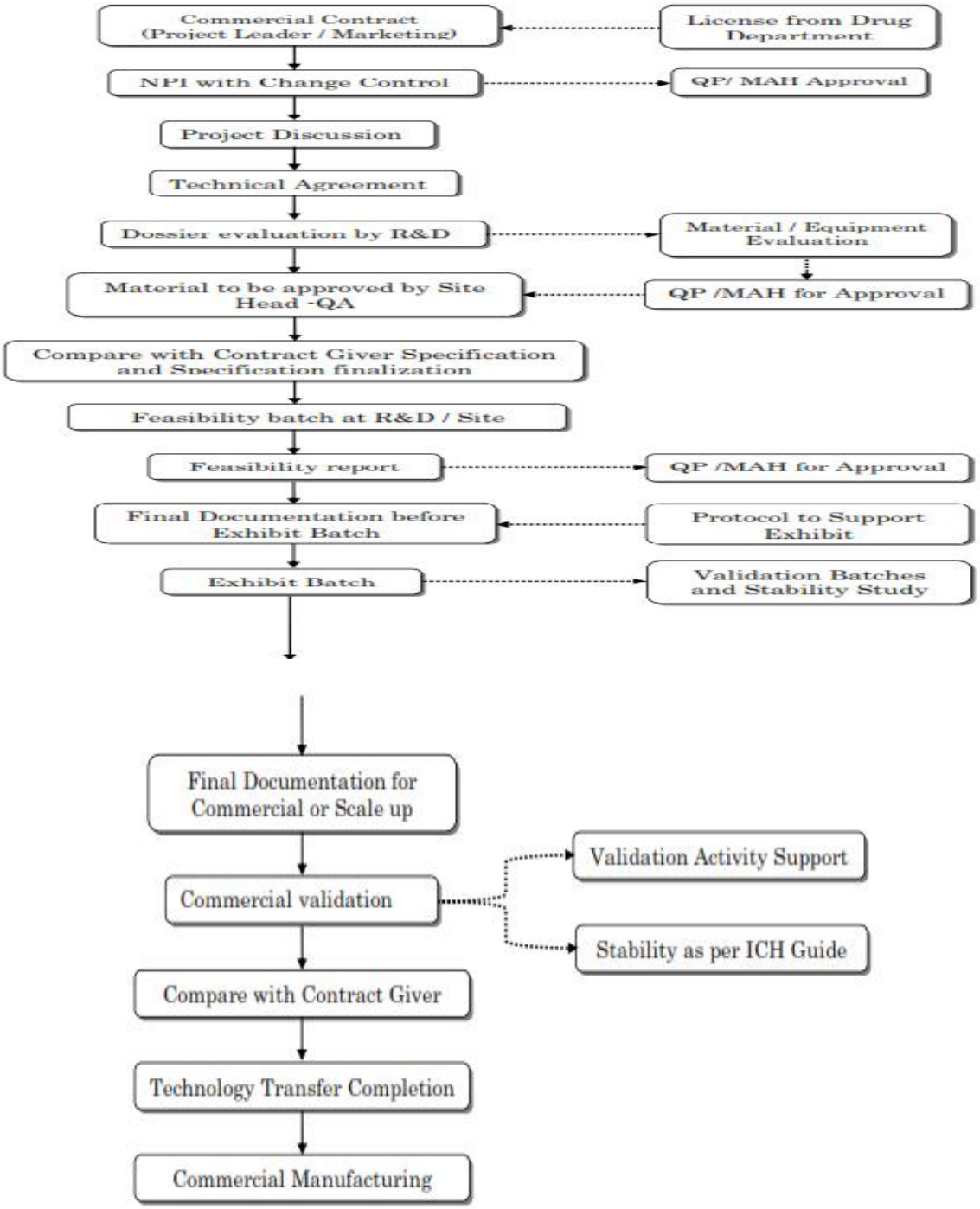
SR. NO.	QUESTION ANSWER
8.0	**CAPA**
8.1	**Correction** Immediate action to correct **Corrective Action** Action required to correct and prevent a re-occurrence for something that happened yesterday **Preventive Action** Action required to prevent an occurrence of something that may happen tomorrow **Root Cause Analysis :** Root cause analysis is a problem solving technique for identifying the basic or cause factor (s) that underlie the occurrence or possible occurrences of an adverse event in a process similar to diagnosis of disease – with the goal always in mind of preventing reoccurrence. **CAPA Identification** The source of quality problems leading to CAPA could be following, but not limited to: ➢ Change Control and its trends ➢ Deviations/Incidents and its Trend ➢ Market Complaints and its Trend ➢ Out of Specification Results and its Trend ➢ Stability Results, Out of Trends ➢ Product Recalls and/or Field Actions, such as Field Alert Reports ➢ Material / Batch Failure, Self Inspection/Audits ➢ Regulatory Audit and Commitments (Query/deficiency received post submission to any regulatory agency) ➢ Audit by Contract Giver ➢ Technology Transfer Document ➢ PQR, Environment and its Safety ➢ Quality Control Stability Reports ➢ Return Goods, Other Non Conformances ➢ Risk Assessment ➢ Recommendation of Executed Validation ➢ Adverse Reaction Reported, Supplier Non Conformance ➢ Process Control Data Review ➢ Instrument/Equipment Service Data Review ➢ Calibration Review, Management Review Results ➢ Scrap, Yield or Rework Data Any Assessment of Quality data that reveals a negative trend, undesirable condition, out of control situation or other Quality problem may result in a CAPA. All CAPA form shall be maintained separately with CAPA log by designated QA person, for easy traceability.

SR. NO.	QUESTION ANSWER

FLOW CHART OF CAPA



SR. NO.	QUESTION ANSWER
9.0	**MANAGEMENT NOTIFICATION**
9.1	**FLOW CHART FOR MANAGEMENT NOTIFICATION** 

SR. NO.	QUESTION ANSWER
10.0	**NPI**
10.1	**FLOW CHART OF NPI** 

SR. NO.	QUESTION ANSWER
11.0	**REGULATORY UPDATES**

11.1

SR. NO.	NAME OF THE REGULATORY AGENCY	WEBSITES
1	DCGI (India)	www.cdsco.nic.in
2	WHO	www.who.int
3	ICH	www.ich.org
4	PICs	www.picscheme.org
5	USFDA	www.fda.gov/drugs
6	Health Canada (Canada)	www.hc-sc.gc.ca
7	MHRA (Europe)	www.mhra.gov.uk
8	EMEA (Europe)	www.ema.europa.eu
9	EDQM (Europe)	www.edqm.eu
10	MCC (South Africa)	www.mccza.com
11	TGA (Australia)	www.tga.gov.au
12	ANVISA	www.anvisa.gov.br/eng/index.htm

Head –QA/designee shall subscribe to receive the periodic updates and changes of regulatory guidance from various regulatory agencies at the following web addresses, where such subscription is not available, specific website shall be checked for any updates.

Regulatory guidance updates shall be reviewed and downloaded by visiting the web sites mentioned above. Latest regulatory guidance/addendum to guidance can be downloaded from publications/news centers/consumer updates/public health notifications/latest press etc.

Head QA/designee shall compile the updates and relevant changes and communicate to all affecting departments once in a month

RA, R&D, Marketing and Purchase departments shall also be informed by Head-QA for the regulatory updates/relevant changes,

After receiving news letter/updates/information from QA, all affecting departments head shall evaluate the system by performing gap analysis against the updated guidance

SR. NO.	QUESTION ANSWER
	Affecting departments head shall share the gap analysis details with Head-QA and implement the changes through change control procedure. Head –QA shall share regulatory updates/news letters, gap analysis and its implementation to Head-CQA on monthly basis. Head-QA/designee shall provide training to the concern department about the regulatory updates/changes before its implementation, where applicable.
12.0	**PLANT QUALITY REVIEW MEETING**
12.1	It is a meeting conducted every month at location of Medley pharmaceuticals Ltd, Daman to discuss the key performance indicators (KPIs) of total Quality Management tools with the help of prepared metrics. Cross functional HOD's from each department shall be a part of the meeting to discuss and conclude the actions of KPIs. A schedule for Plant Quality Review Meeting (PQRM) shall be followed every year as per the **Annexure- I**. This review meeting shall be held on every month within the second week. The Annual schedule shall be prepared by Manger- QA and approved by Head- QA. The meeting shall emphasize effective understanding of Quality GMP issues that shall result in effective decision out come. Based on the discussion held in the plant quality review meeting action plan, responsible person and target completion date shall be decided by the user departments Head and shall be documented in minutes of meeting Head –QA/Designee shall share the outcome and minutes of meeting with the all respective department head and to Senior Management on agreed actions.

SR. NO.	QUESTION ANSWER
13.0	**SHELF INSPECTION**
13.1	A systematic inspection program to detect any short comings in the implementation of cGMP and to recommend necessary corrective actions. Manager QA/Head QA shall nominate the Self Inspection team. Team shall be a cross functional team comprising of persons from different departments such as Quality Assurance, Quality Control, Production, Warehouse, Engineering and Personnel and Administration department . QA must be a part of the team. Internal auditor shall be trained with Auditor certification Training program. Educational Qualification: Graduate in Science, Pharmacy, Engineering and other respective disciplines. Experience: Preferably 5 years of experience in pharmaceutical industry, GMP knowledge, professional and practical experience related to GMP. Understanding of National, Local and Global legislation GMP. Designate QA person shall prepare a schedule (for the next year) at the end of the calendar year The frequencies for audit shall be scheduled as twice in a year The actual audit date may vary by ± 15 working days from the tentative date or depend on the availability of Audit team. The Self Inspection team shall summarize the audit observations and discuss the observations among the team members. The team shall classify the audit observations as Critical, Major or Minor based on following. The concerned HOD shall submit the response within 10 working days of receipt of "Self Inspection observation report" which includes compliance to audit observations, action plan for CAPA with target completion date. The self-audit team members shall review the compliance report and verify the implementation as stated in the compliance report. On verification of implementation, the self-audit team members shall close the report and submit the report along with Audit summary (Annexure II) to Head - QA. Head - QA/ Designee shall review and ensure that the observation reports are closed properly Designated person from QA shall store the report in documentation cell for 6 years.

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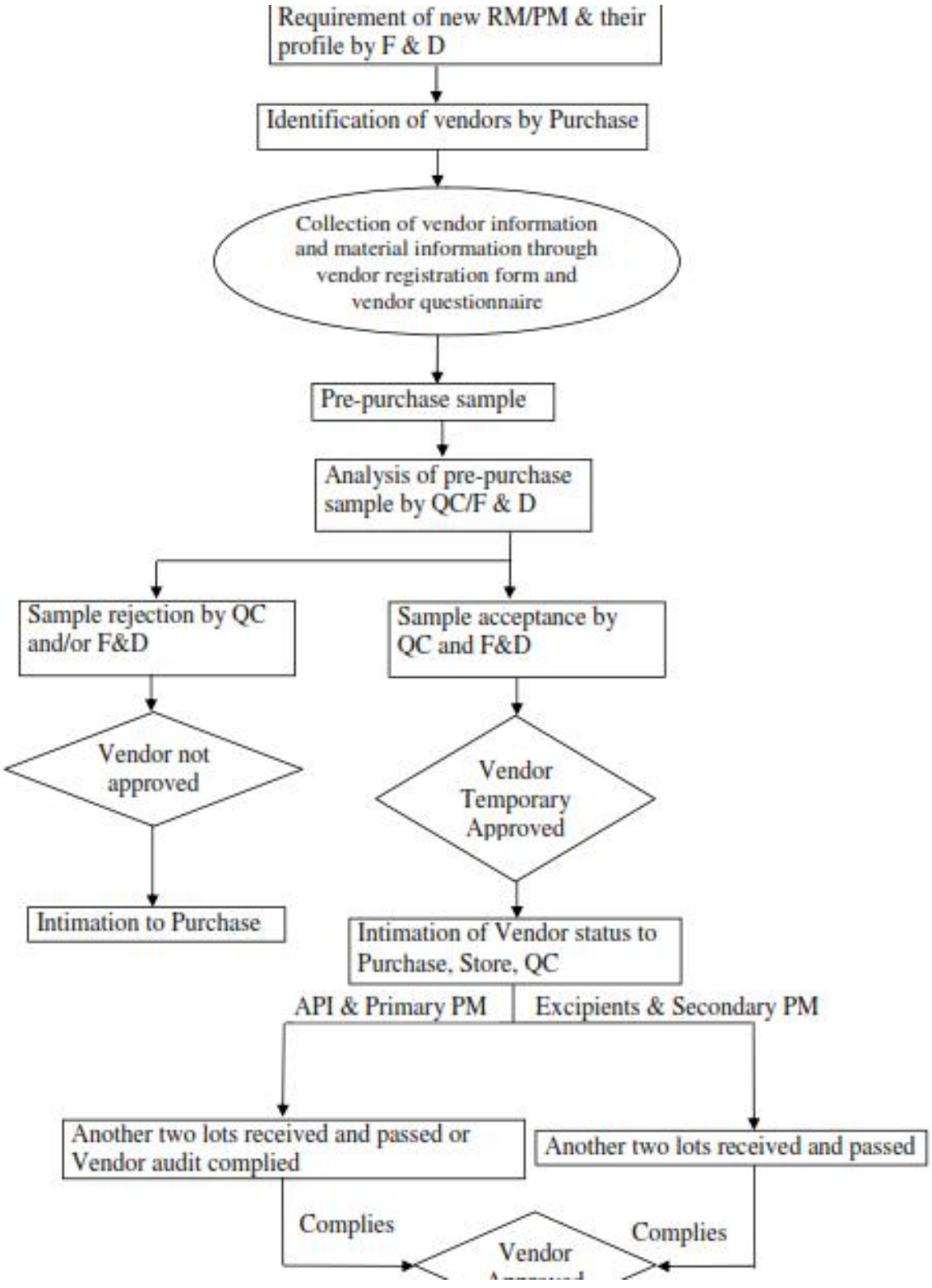
SR. NO.	QUESTION ANSWER
14.0	**VENDOR MANAGEMENT**
14.1	**DEFINATION:** **New Vendor:** Manufacturer identified by Formulation Development or purchase department as a manufacturer to supply of a specific material from a specific manufacturing site. **Approved Vendor:** Manufacturer of raw material, primary and printed packaging material, which has been approved by QA to supply a specific material from specific site, based on the satisfactory cGMP history as well as compliance of material to specification. **PROCEDURE:** **VENDOR DEVELOPMENT** The requirement of new raw & packing materials and their profiles shall be given by the formulations development department. In charge-purchase (Vendor development) shall identify the vendors with the available information based on specifications provided by formulations development department. **ASSESSMENT OF NEW VENDOR (S) FOR NEW / EXISTING MATERIAL** **TEMPORARY APPROVED VENDORS** In order to select a new vendor, evaluation of the manufacturer's capability, service performance and quality history is required. Purchase department shall collect and maintain information of the new vendor through the vendor registration form for manufacturer and for supplier or Trade. Purchase department will get technical information regarding the material through vendor questionnaire from the vendor which includes the brief manufacturing process, TSE/BSE free declaration, impurity profile, residual solvent information, GMO free declaration, Melamine free declaration, Gluten free declaration and stability data/shelf life statement etc. as applicable depending upon the type of material. **GMO : Genetically Modified Organism** *Note: For non-critical excipients requirement of impurity profile, residual solvent information, stability data, GMO/Melamine/Gluten free declarations are not mandatory.* *Purchase department shall ask the vendor for analytical method and analytical method validation data for the materials claiming residual solvents.* Based on the evaluation of above information and vendor registration form, Purchase/Formulation development department shall ensure that vendor is ready to supply material of required grade with specific requirement, if any.

SR. NO.	QUESTION ANSWER
	Purchase department shall ask the vendor for pre-purchase samples of at least one batch depending upon the along with its certificate of analysis and shall be sent to Formulation Development and/or Quality Control for analysis. Formulation Development and/or Quality Control shall evaluate the source material lots and on compliance of the sample as per specification and shall confirm the suitability as per specification to purchase department. Formulation Development and/Quality Control will intimate the purchase and QA for suitability of sample. Based on the assessment report from Formulation Development and/Quality Control satisfactory evaluation of data provided by the vendor, the new vendor shall be considered as a **'Temporary Approved'.** The vendor list contains Material Code, Material Name, Synonym/ Storage Condition, Manufacturer Name and Site Address, Suppliers Name and Address and current approval status. The vendor list shall be prepared, reviewed and approved**.** A separate vendor list shall be prepared for US/UK market and others. Once vendor is temporary approved, vendor code is to be assigned to the particular vendor as well as material code in SAP is to be generated by purchase department in co-ordination with SAP department. **APPROVED VENDORS** Temporary approved" vendor becomes "Approved" vendor if following conditions are met- **For Manufacturer** Another Two commercial lots supplied by Temporary approved vendors are analysed and passed. In case of API/ Primary packing material, vendor questionnaire is filled and vendor audit is done and complied. In case of excipients and secondary packing material questionnaire is completed.(if required, audit to be carried out) When manufacturing site audit is required, it shall be carried out by site QA/CQA to assess compliance with cGMP requirements. The manufacturing site of the vendor shall be audited as per the checklist. Based on the audit findings, a detailed report shall be classified as critical(C), Major (M) and minor (N) as described under definitions. The purchase department shall send the site audit report prepared by site QA/CQA to the vendor. The vendor should respond in a period of 30 days after receipt of the audit report from purchase department.

SR. NO.	QUESTION ANSWER
	The audit compliance report received from the new vendor shall be evaluated by the audit team members and recommendations shall be given to approve or reject the vendor by head QA. Re-audit may be required for ensuring compliance in case of critical deficiencies observed during the audit. QA shall update the vendor list once in 6 months to include or exclude approved vendor and to reflect the change in the status of vendors. **PERIODIC EVALUATION OF APPROVED VENDORS** For approved vendor's evaluation, following steps shall be followed: Evaluation of the vendor's quality performance shall be done once in a year. This annual evaluation shall include review of rejection rate of the vendor's lots and resolution of quality issues, if any Yearly trending of all API from the Vendor shall be carried out of quality issues, if any. Reassessment of quality systems shall be carried out if the rejection rate on quality grounds is higher than 20%. All the vendor's of API and primary packing materials shall be audited once in three years. The vendor should respond with audit compliance report in a period of 30 days after receiving the audit report from purchase department. If the compliance is not satisfactory, then the vendor rating will be downgraded or disapproved and deleted from the list. QA will update the vendor list accordingly and communication of the same shall be sent to QC, warehouse and purchase department. **DISQUALIFICATION OF VENDORS** Vendors failing to meet the GMP requirements and those consistently (up to three lots) failing to meet quality standards shall be disqualified and blocked for supply of material by QA. However vendor can immediately be disqualified, Incase of any critical failure e.g. failing in potency (Assay below 80 %), microbial test (failure in pathogens). If the satisfactory corrective actions are taken by the vendor to resolve the quality problems and non-compliances, the vendor shall be re-approved for the supply.

SR. NO.	QUESTION ANSWER

FLOW CHART OF VENDOR APPROVAL



SR. NO.	QUESTION ANSWER
15.0	**CLEANING VALIDATION**

15.1

GUIDELINE :
Health Products and Food Branch Inspectorate Cleaning Validation Guideline- Health Canada.

DEFINATION:

Cleaning Validation: Cleaning validation is documented evidence that an approved cleaning procedure will provide equipment which is suitable for processing medicinal products.

Types of contaminants

- Chemical - Residues of the previous product
- Biological - Microorganisms
- Physical - Particulate matter

Solubility of API shall be mentioned as per following Table:

Solubility	Approximate volume of solvent in milliliters per gram of solute
Very soluble	Less than 1 part (< 1)
Freely soluble	From 1 to 10 parts (1 : 10)
Soluble	From 10 to 30 parts (10 : 30)
Sparingly soluble	From 30 to 100 parts (30 : 100)
Slightly soluble	From 100 to 1000 parts (100 : 1000)
Very slightly soluble	From 1000 to 10000 parts (1000 : 10000)
Practically insoluble	More than 10000 parts (> 10000)

LD50 of API shall be mentioned as per following Table:

Probable oral Lethal dose for humans (Mg/ kg)	Included descriptive terms
>15000	Practically non toxic
5000-15000	Slightly toxic
500-5000	Moderately toxic
50-500	Very toxic
5-50	Extremely toxic
<5	Super toxic

SR. NO.	QUESTION ANSWER

Cleanability of API shall be mentioned as per following Table:

Solubility	Approximate volume of solvent in milliliters per gram of solute	Cleanability Index
Very soluble	Less than 1 part (< 1)	Easily cleanable
Freely soluble	From 1 to 10 parts (1 : 10)	Easily cleanable
Soluble	From 10 to 30 parts (10 : 30)	Easily cleanable
Sparingly soluble	From 30 to 100 parts (30 : 100)	Hard to clean
Slightly soluble	From 100 to 1000 parts (100 : 1000)	Hard to clean
Very slightly soluble	From 1000 to 10000 parts (1000 : 10000)	Mechanical water forced required
Practically insoluble	More than 10000 parts (> 10000)	Mechanical water forced required

All equipments parts shall be identified as per rational criteria and categories as per bellow

- Hard to clean
- Direct contact with product
- No direct contact with product

SAMPLING TECHNIQUES

Visual Inspection (Method For Validation of Cleaning of Equipments):

After cleaning of the equipment visual inspection shall be done using a torch held inclined to the surface being inspected, and a mirror (attached to stainless steel rod) to inspect the surface of equipment. Visual inspection shall be done by unaided naked eye.

For visual cleaning;

Verify the cleanliness of the product contact surfaces.

Verify the cleanliness of hard to clean areas.

Verify all the product contact dismantled parts before and after assembling.

Surface Swab Sampling:
The direct Sampling technique is also commonly referred to as “Direct Surface Sampling” method. This is done by Swabbing Technique using Swabs. The direct surface sampling method is the preferred technique.

SR. NO.	QUESTION ANSWER

Sampling Procedure:

Surface sampling is identified as a sampling method considering the design, size and number of equipment.

After the completion of equipment cleaning, visual inspection shall be done.

In case, the surface of equipment is difficult to inspect, a mirror attached to a stick shall be used to inspect the cleanliness of equipment.

Complete product contact surface area shall be sampled for critical hard to clean area/ critical accessories like spray gun, punch, dies, and butter fly valve etc.

Swab Sampling for Chemical analysis:

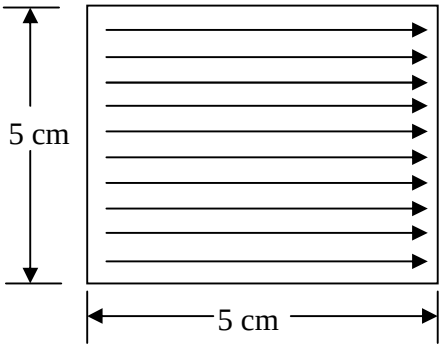
After visual inspection is found satisfactory swab sampling shall be carried out.

Wear hand gloves and nose mask before commencing swab sampling.

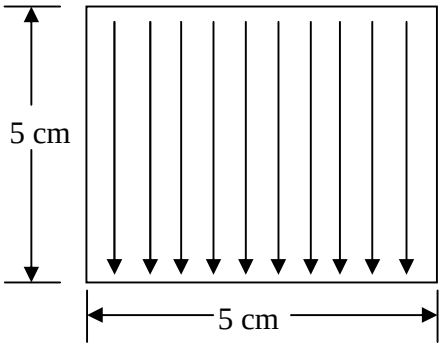
The swab must be wetted in purified water or suitable diluents.

Swab area shall be measured with the help of template for swabbing and the area must be 5cm x 5cm or as per protocol.

Swabbing shall be done by parallel horizontal and then tilt the swab and do vertical strokes as described below to assure that the entire area is swabbed.



Horizontal strokes



Vertical strokes

After swabbing, place the swab into a stoppered test tube, wrap with aluminum foil and label the test tube for identification of swab sample.

Swab samples must be collected from different areas of equipment as stated in the cleaning validation protocol.

Send the stoppered test tube with swab to Quality Control Laboratory for analysis.

Swab sampling for Microbial analysis:

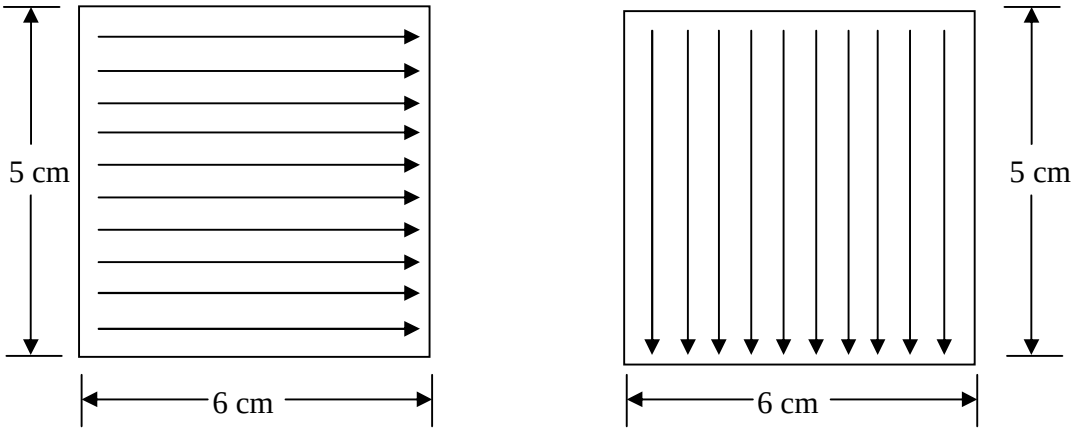
Wear sterile hand gloves and nose mask before commencing swab sampling to avoid the microbiological contamination.

Sterile cotton swab shall be used for swabbing.

SR. NO.	QUESTION ANSWER

The sterile cotton swab shall be soaked in sterile saline.

Swabbing shall be done by parallel horizontal and then tilt the swab and do vertical strokes as described below to assure that the entire area is swabbed.



Horizontal strokes Vertical strokes

Swab area shall be measured for swabbing and the area must be 5cm x 6cm.

Microbial swab sample shall be collected before chemical swab.

Swabbing shall be done on the surface of equipments and the area is different from the area of swab taken for chemical analysis.

After swabbing, place the swab into a sterilized stoppered test tube and label the test tube for identification of swab sample.
Swab samples must be collected from different areas of equipment as stated in the cleaning validation protocol.

Send the sterile stoppered test tube with swab to Quality Control – Microbiology Laboratory for analysis.

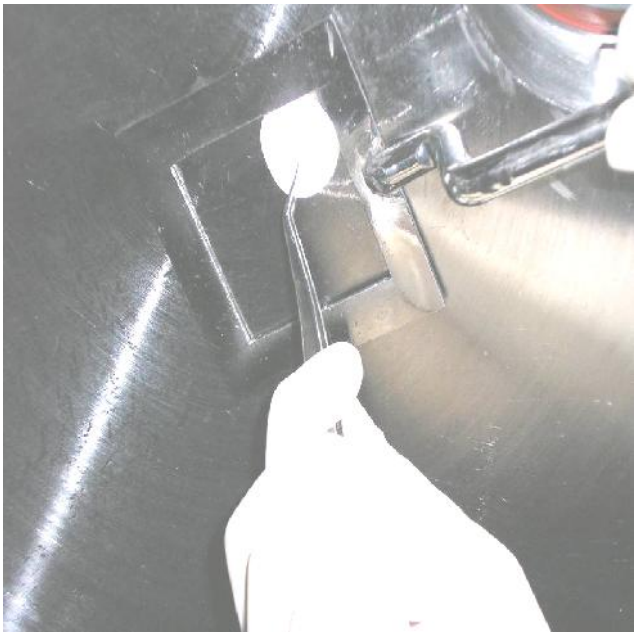
Rinse Sampling Procedure:
After visual inspection is found satisfactory, the equipment shall be rinsed with the volume of rinsing solvent (purified water) as described in respective cleaning validation protocol (rinse sample shall be performed whenever necessary).

Rinse sample shall be collected in the bottles used for the collection of routine purified water samples.

After the collection of rinse sample, (stopper) close the bottle and label it for identification of rinse sample.
Send the rinse sample bottle to Quality Control Laboratory for analysis.

SR. NO.	QUESTION ANSWER

MANUFACTURING VESSEL LID



GASKET





MFG VESSEL LID



PRODUCT CONTAINER LID

SR. NO.	QUESTION ANSWER

Method of analysis:

Methods of analysis used for determination of possible contaminant residues must be specific and sensitive.

The selection of analytical methods shall be validated for at least below mentioned parameters based on at least the following but not limited to;

- Precision,
- Specificity
- Linearity and Range,
- Limit of Detection,
- Limit of Quantification,
- Stability of solutions,
- Recovery from Equipment Surface.

FOR WORST CASE APPROACH;

10 PPM Criteria:

$$MACO = \frac{[Mac10] \times [Swab\ Area]}{[Shared\ equipment\ surface\ area\ between\ products]}$$

Where,
Mac10 = 10 ppm x Minimum Batch Size of Product 'B' in kg.

Dose Criteria:

$$MACO = \frac{S.F \times [SRDD\ (A)\ in\ mg] \times [MBS\ (B)\ in\ mg] \times [Swab\ Area]}{[LRDD\ (B)\ in\ mg] \times [shared\ equipment\ surface\ area\ between\ products]}$$

Where, A = Product to be cleaned.
B = Product to be manufactured.
S.F. = Safety factor (value based on dosage form/route of administration)
SRDD (A) = Smallest recommended Daily Dose of Product "A" in 'mg'
LRDD (B) = Largest recommended Daily Dose of Product 'B' in mg.
MBS (B) = Minimum Batch Size of Product 'B' in mg.

SR. NO.	QUESTION ANSWER

Calculate maximum allowable carry over (MACO) of active residue for rinse analysis:

$$MACO = \frac{S.F \times [SRDD\ (A)\ in\ mg] \times [MBS\ (B)\ in\ mg] \times [RS\ sample\ volume]}{[LRDD\ (B)] \times [shared\ equipment\ volume\ between\ products]}$$

Where,

A = Product to be Cleaned

B = Product to be manufactured.

S.F. = Safety Factor (value based on dosage form / route of administration)

SRDD (A) = Smallest Recommended Daily Dose of Product 'A' in mg

LRDD (B) = Largest Recommended Daily Dose of Product 'B' in mg.

MBS (B) = Minimum Batch Size of Product 'B' in mg.

ACCEPTABILITY LIMITS:

Visual inspection criteria: No quantity of residue should be visible to naked eyes on the equipment after cleaning procedures are performed (i.e. less than 100 mcg /25 cm^2).

10ppm criteria: Not more than 10ppm of active pharmaceutical ingredient of previous product is permitted in next product.

Dose based criteria: Not more than 1/1000 of minimum daily therapeutic dose of the previous product in the maximum daily dose of the next product

The acceptability limits for microbiological sample shall be determined based on;

Parameters	Limit Dirty Equipment Surfaces	Limit Cleaned Equipment Surfaces
Total Aerobic Microbial Count (TAMC)	NMT 1000 cfu/swab	NMT 100 cfu/ swab
Total Combined Yeasts and Molds Count (TYMC)	Less Than 10 cfu/swab	Less Than 10 cfu/ swab

SR. NO.	QUESTION ANSWER

Re-validation:

Re-validation shall be performed in case of any change, (at least the following but not limited to)

- Introduction of a new facility, equipment, process or product.
- Change in cleaning procedure.
- Change in cleaning agent used for cleaning.
- Reduction in minimum batch size and lowest dose of the product i.e change in MACO limit.
- Major Modification in processing equipment.
- Periodic revalidation after every three years.
- Change in regulatory requirements.

Dirty Equipment Hold Time (DEHT) – The time from the end of manufacturing till the beginning of the cleaning process of equipment (also called things like "soiled hold time")

The Hold Time Study of Dirty Equipments shall be carried out by keeping equipment in idle for a period of 24 hours in dirty condition. (The Maximum possible hold period under normal conditions) to evaluate microbial contamination on equipment surface and effectiveness of cleaning process.

Clean Equipment Hold Time (CEHT) – The time from the end of equipment cleaning till subsequent use of equipment (subsequent use includes product manufacturing).

The Hold Time Study of Clean Equipments shall be carried out after completion of "Type B Cleaning", visual inspection by keeping equipment in idle clean condition up to 72 hours to establish the expiry of cleaning in view of microbiology.

After the equipments surfaces are found visually clean, sampling and testing shall be carried out for Microbiological enumeration Tests and residual determination (chemical analysis) on the cleaned equipment surfaces at 0 hour interval, then sampling and testing shall be carried out only for Microbiological enumeration Tests at rest intervals as per the sampling plan. (i.e., after 24 hours, 48 hours and 72 hours).

Dirty Equipment Hold Time Period : 24 Hours

Cleaned Equipment Hold Time Period : 48 Hours

SR. NO.	QUESTION ANSWER
16.0	**PRODUCT QUALITY REVIEW (PQR)**
16.1	**DEFINATION:** **PRODUCT QUALITY REVIEW (PQR)**: Documented regular periodic or rolling quality reviews of all licensed medicinal products with the objective of verifying the consistency of the existing manufacturing process to highlight any trends and to identify product and process improvements or weaknesses for licensed medicinal products the appropriateness of current specifications for both starting materials and finished products is included **PROCEDURE:** PQR shall be prepared for each product manufactured and tested in a calendar year from January to December. The Final PQR shall be prepared before the end of first quarter of the next year i.e. 31st March. Interim PQR shall be prepared as trend of critical parameter on every four months i.e. January- April, May-August, September – December. Trend data for critical in process parameters, finished product, analytical parameters and process parameters shall be prepared and reviewed. Critical parameters such as, **In-Process Parameter includes** (but not limited to), Average weight, pH, Water Content, Hardness, DT & Friability, and Assay etc. **Finish Product Tests includes** (but not limited to), Assay, Water / Loss on Drying, Identification, Description, PH, Fill volume, related substances Dissolution, etc. **Process parameters includes** (but not limited to), Blending time, mixing time, RPM of compression machine, details of yield reconciliation of total batche manufactured in the year. Graphical representation for trend data of in process Parameters, Finished product analytical parameter and Process Parameters shall be made.Following statistical quality review shall be performed on critica parameters e.g. • Minimum, Maximum & Mean value of analytical parameter. • Standard Deviation • Relative Standard Deviation • Process Capability (CpK)

SR. NO.	QUESTION ANSWER

Process Capability (CpK) shall be carried out for critical analytical parameters e.g. Assay.

$$CpK = \frac{USL - X}{3*SD} \quad \text{or} \quad \frac{X - LSL}{3*SD}$$

Where LSL = Lower specification limit

USL = Upper specification limit

X = mean

SD = Standard Deviation

This calculation helps to understand how close the process is producing outcomes compared to what th specification is.

Interpretation:

CpK < 1.0 i.e. process is not capable

CpK 1.00 to 1.33 i.e. product is barely manufactured

CpK 1.34 to 3.00 i.e. process is good

CpK > 3.0 i.e. Process is excellent

Note: Minimum 10 batches are required to calculate the Process Capability (CpK).

Storage Period
All PQR is to be stored for the period of six years.

What is PQR :

Which name is using in MHRA/USA –PQR/APQR

Which guideline

EudraLex Volume 4
Health Science Authorities (HSA)
PICS

If OOT found then
If any abnormal trend of the data observed during the compilation and review, it shall be commented in the report, if required the investigation shall be done.

PHARMA BOOK

SR. NO.	QUESTION ANSWER

CONTENTS

Review of starting material
Review of packing material
Review of critical in-process controls
Review of finished product results
Review of process parameters
Review of all batches that failed to meet established specification and their investigation
Review of significant deviations or non-conformance.
Review of changes
Review of marketing authorization variation
Review of stability monitoring program and adverse trends
Review of quality related complaint/recall /any investigation conducted.
Review of adequacy of any other previous product process/equipment corrective actions
Review of new marketing authorization and variations and review of post marketing commitments
Review of qualification status of relevant equipments and utilities
Review of technical agreements
Review of process validation
Review of control sample evaluation
Review of environmental and water quality status
Process capability
Summary
Conclusion
Recommendation
List of Annexures Attached
Reference
Abbreviations

SR. NO.	QUESTION ANSWER
17.0	**PROCESS VALIDATION**
	DEFINATION: **Process Validation**: Process validation is establishing documented evidence which provides a high degree of assurance that a specific process will consistently produce a product meeting its pre-determined specifications and quality characteristics. **Types of Validation** • Prospective Validation • Concurrent Validation • Retrospective Validation • Revalidation **Prospective Validation**: Validation carried out during the development stage by means of a risk analysis of the production process, which is broken down into individual steps. These are then evaluated on the basis of past experience to determine whether they may lead to critical situation. **Concurrent Validation**: Validation carried out during routine production of product intended for sale on at least one batch.
17.1	**Retrospective validation (Based on Historical data):** This approach to validation shall be undertaken on products already in commercial distribution and have a long history of compliance to established standards. **Re-validation:** A repeat of the process validation to provide an assurance that changes in the process/equipment introduced in accordance with change control procedures do not adversely affect process characteristics and product quality. **PROCEDURE:** Process Validation shall be carried out in the following cases : • New product introduction • Change in manufacturing formula • Change in approved vendor source of active pharmaceutical ingredient • Change in Batch size. Change in Equipment. Change in Manufacturing site • Any other change as deemed necessary for validation through change management system The Process validation shall be performed on at least three successful commercial batches or as per respective country's regulatory requirement

SR. NO.	QUESTION ANSWER

In case where the circumstances demands single or two batches, the process validation shall be carried out covering all the variables [Critical quality attributes (CQA) and critical process parameters (CPP)] and a final report shall be prepared based on the single or two batches data.

In case where the process validation is planned for three batches but circumstances demands batch release prior to completion of all three validation batches then an interim report shall be prepared

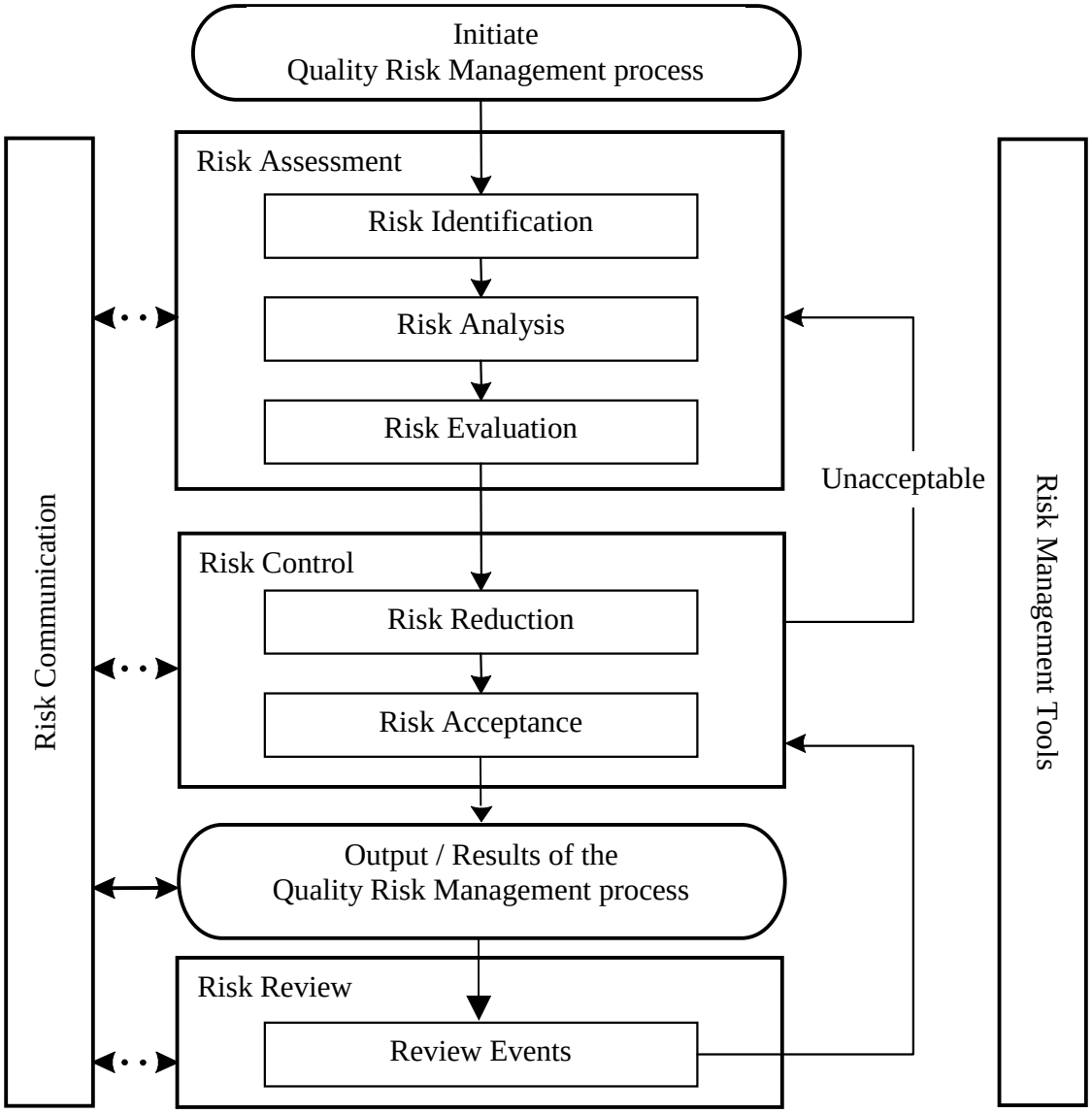
Prior to progression of exhibit / process validation studies, ensure the following availabilities:

- All instruments are calibrated.
- All equipments, utilities and area are qualified.
- All personnel are trained and qualified.
- Process validation protocol is approved.

Contents

- Product Details
- Protocol Approval Sheet
- Contents of process validation protocol
- Introduction,
- Objective,
- Scope
- Responsibilities
- Number of Process Validation batches
- Design Plan
- Reference Documents
- List of Equipments
- Qualification of Equipment
- In-process testing instrument details
- Process Flow Chart
- Manufacturing Process
- Scientific justification for critical process parameters
- Composition
- Sampling plan
- Certificate of Analysis
- Acceptance Criteria
- Change control and revalidation criteria
- Deviation
- Summary Report, Conclusion and Approval
- List of Annexure

SR. NO.	QUESTION ANSWER
	Any Out of Specifications encountered during the process validation execution shall be investigated and the process validation program shall be modified if required. **REVALIDATION** • Change in Batch Size. • Change in location of product manufacturing site. • Change in Major Equipment or major part of the equipment impacting the product quality. • Change in manufacturing formula. • If there is any change in the Regulatory requirements. • Change in API source. • As per review recommendation in APR.

SR. NO.	QUESTION ANSWER
18.0	**QUALITY RISK MANAGEMENT**
18.1	**DEFINATION:** **Risk Assessment:** A systematic process of organizing information to support a risk decision to be made within a risk management process. It consists of the identification of hazards and the analysis and evaluation of risks associated with exposure to those hazards. **General Quality Risk Management Process** 

SR. NO.	QUESTION ANSWER

Quality risk management team shall be a cross functional team comprise of experts from different areas (such as Head-QA/designee (as a team Leader), Quality Assurance, Quality Control, Production, Warehouse, Engineering departments, P&A, Regulatory affairs, ADL, R&D and Marketing department) in addition to individuals who are knowledgeable about the quality risk management process.

Risk Identification:
Risk may be identified by anyone working in his/her respective workplace with the systematic use of information.

Risk Analysis :
Team shall analyze the risk linking the likelihood of occurrence, detection and severity of harm using qualitative descriptor such as "High", "Medium" and "Low".

Relative Risk	Description
High	The Operation / Practice /Equipment/ Condition / System/ Documents/ Materials etc. that may have direct impact on product quality/ safety. Failure of the system which may result in an inappropriate decision or action related to product quality/ safety. There is no other system to check or verify the product quality/ safety.
Medium	The system can have an indirect impact on product quality/ safety. Failure of the system may result in an inappropriate decision or action relative to supporting processes or systems that have direct impact on product quality/safety.
Low	1) The system does not have an impact on product quality. Failure of the system may result into changes in practices, Procedure, SOP modification etc with no risk to product quality/ safety.

Risk Evaluation :
Risk shall be evaluated by considering the probability of occurrence, detectability and severity of the harm covered under Risk Management Tools.

Risk Control
Quality Risk management team shall decide the steps to control the risk by considering the following:

- Is the risk estimated in the assessment above an acceptable level?
- What can be done to reduce or eliminate the risk?
- What is the appropriate balance among benefits, risk and resources?
- Are new risks introduced due to identified risk being controlled?

Based on the criticality or level of risk, specific corrective actions should be developed to prevent recurrence of instances where there have been deviations from established risk control measures, especially for high risks

SR. NO.	QUESTION ANSWER
	Risk Acceptance: If it is not possible to entirely eliminate the risk, decision shall be taken to accept the risk assuring to reduce it to acceptable level. This acceptable level will depend on many parameters and should be decided on a case to case basis. The Quality risk management team shall identify the corrective actions for the identified failure or failure. The Quality risk management team shall draw out the conclusion at the end of the quality risk assessment study. **Risk Communication:** Risk communication is information sharing session between risk management team and other concern department involved with different functions. Once approved, quality risks shall be communicated to the relevant department Heads to implement the suggested actions to mitigate / avoid risks. Training shall be given to the concern to mitigate/ avoid risks. If required, risk shall be communicated to the suppliers/customers. The output / results of the risk management shall be appropriately communicated and documented. **Risk Review:** Risk assessment reports along with supporting documents (if any) shall be forwarded to respective head of the department for review. Further same reports shall be forwarded to Head — QA for review and approval. Identified quality risks through Planned Risk assessment (e.g. change control, temporary change etc.) and Unplanned Risk assessment (e.g. deviation, complaint, OOS etc) shall be logged and tracked in "Risk Management Log.. Risk assessment reports and risk management log shall be maintained by QA. As an ongoing part of quality management process, risk management shall be reviewed to take into account new knowledge and experience. Once Quality risk management process has been initiated, the process shall be utilized continuously by QRM team, for events that might impact the original quality risk management decision whether these events are planned (e.g. results of product review, change controls, inspections, audits) or unplanned (e.g. Root cause from failure investigation, recall, deviations, complaints). The QRM team shall review and verify for the effectiveness of the process of risk assessment for planned as well as unplanned risks.

SR. NO.	QUESTION ANSWER

Quality Risk Management Methodology

- Basic risk management facilitation methods (flowcharts, check sheets etc.)
- Failure Mode Effects Analysis (FMEA)
- Failure Mode, Effects and Criticality Analysis (FMECA)
- Fault Tree Analysis (FTA)
- Hazard Analysis and Critical Control Points (HACCP)
- Hazard Operability Analysis (HAZOP)
- Preliminary Hazard Analysis (PHA)
- Risk ranking and filtering
- Supporting statistical tools

Failure Mode Effects Analysis (FMEA) :

Selection of the process:
The first thing is, select the process to be analyzed.

Review of the process:
The selected process shall be analyzed and described in a flowchart and flow of the process shall be studied thoroughly for the efficient output. And attach the same to the FMEA.

Brainstorm potential failure modes:
Look at Each stage of the process and identify the ways it could potentially fail or the things that might go wrong.

List of potential effects of each failure mode: List the potential effect of each failure next to the failure. If a failure has more than one effect, mention all. To identify the effects and the causes of the effects "Cause and Effects analysis (fishbone diagram)" can be used.

Assign a severity rating for each effect:
Give each effect its own severity rating (from 1 to 5, with 5 being the most hazardous effect).

Rating	Severity
1	No Effect on output
2	Minor Effect
3	Moderate Effect
4	Serious Effect
5	Hazardous Effect

SR. NO.	QUESTION ANSWER

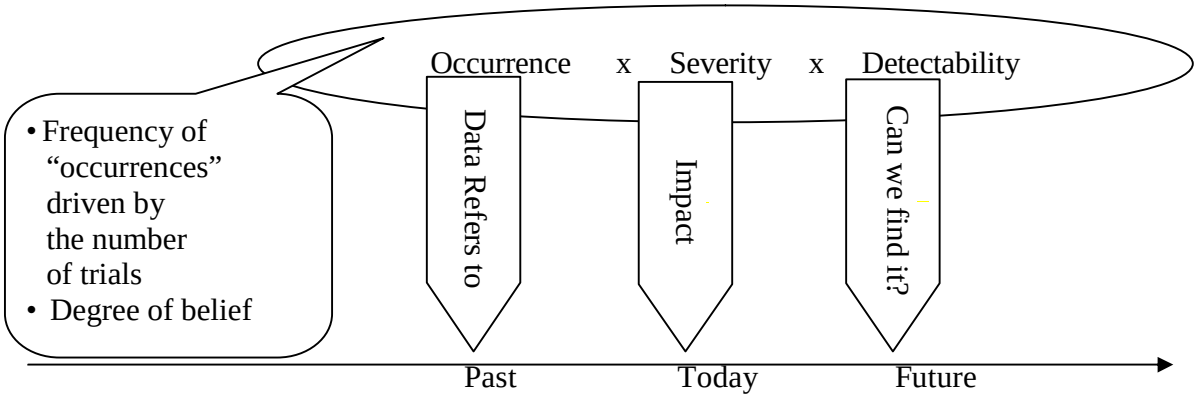
Assign an occurrence rating for each failure mode:
Collect data on the factors responsible for the failure of the product. Using this information, determine how likely it is for a failure to occur and assign an appropriate rating (from 1 to 5, with 5 being the almost certain).

Rating	Occurrence
1	Very rare
2	Unlikely
3	Possible
4	Likely
5	Almost Certain (every time)

Assign a detection rating for each failure mode and effect:
List all controls currently in place to prevent each effect of a failure from occurring and assign a detection rating for each item (from 1 to 5, with 5 being a lack of detection).

Rating	Detectability
1	Always detected
2	Will detect failure
3	Might detect failure
4	Almost Certain not to detect failure
5	Lack of detection control

Calculation of the risk priority number (RPN) for each effect:
Calculate the RPN by multiplying the severity rating with that of occurrence rating and detection rating.



SR. NO.	QUESTION ANSWER

Prioritize the failure modes for action:
Depending upon calculation and analysis carried out, decide the priority order. Give the priority to the items with high RPN value or high severity rate.

Acceptance Criteria:

- In case of calculated RPN rating is greater than 50 that particulars failures are not accepted and recommended solution shall required.
- If the RPN rating is between 25 and 50, recommended solution may be required if the detectability is 5.
- If For RPN rating < 25, no recommended solution is required.
- Recommended solution is required if any of the individual severity, occurrence and detectability is high i.e. 5 (even if RPN is within the acceptance criteria).

Sr. No.	RPN Rating	RPN Category
1	76 to < 125	Critical
2	51 to 75	Major
3	26 to 50	Moderate
4	Up to 25	Minor

Action to eliminate or reduce the high risk failure modes:
The action to be taken for each high risk failure and a person shall be assigned to implement the action /change.

Considering acceptance criteria, detailed recommended solutions to be drawn with responsibility. Implementation should be through appropriate CAPA and change control procedure. Action should be implemented, monitored and reviewed.

Compliance of recommendation shall be monitored by Quality Assurance department.
FMEA shall be reviewed after six months till all RPN are reduced to < 25 or risks are reduced to acceptable level.

SR. NO.	QUESTION ANSWER

Hazard Analysis and Critical Control Points (HACCP):

HACCP is a systematic, proactive and preventive tool for assuring product quality, reliability and safety.

It is a structured approach that applies technical and scientific principles to analyze, evaluate, prevent and control the risk or adverse consequence(s) of hazard(s) due to the design, development, production and use of products.
HACCP is most useful when product and process understanding is sufficiently comprehensive to support identification of critical control points.

The output of a HACCP analysis is risk management information that facilitates monitoring of critical points not only in the manufacturing process but also in other life cycle phases.

HACCP consists of the following seven steps:

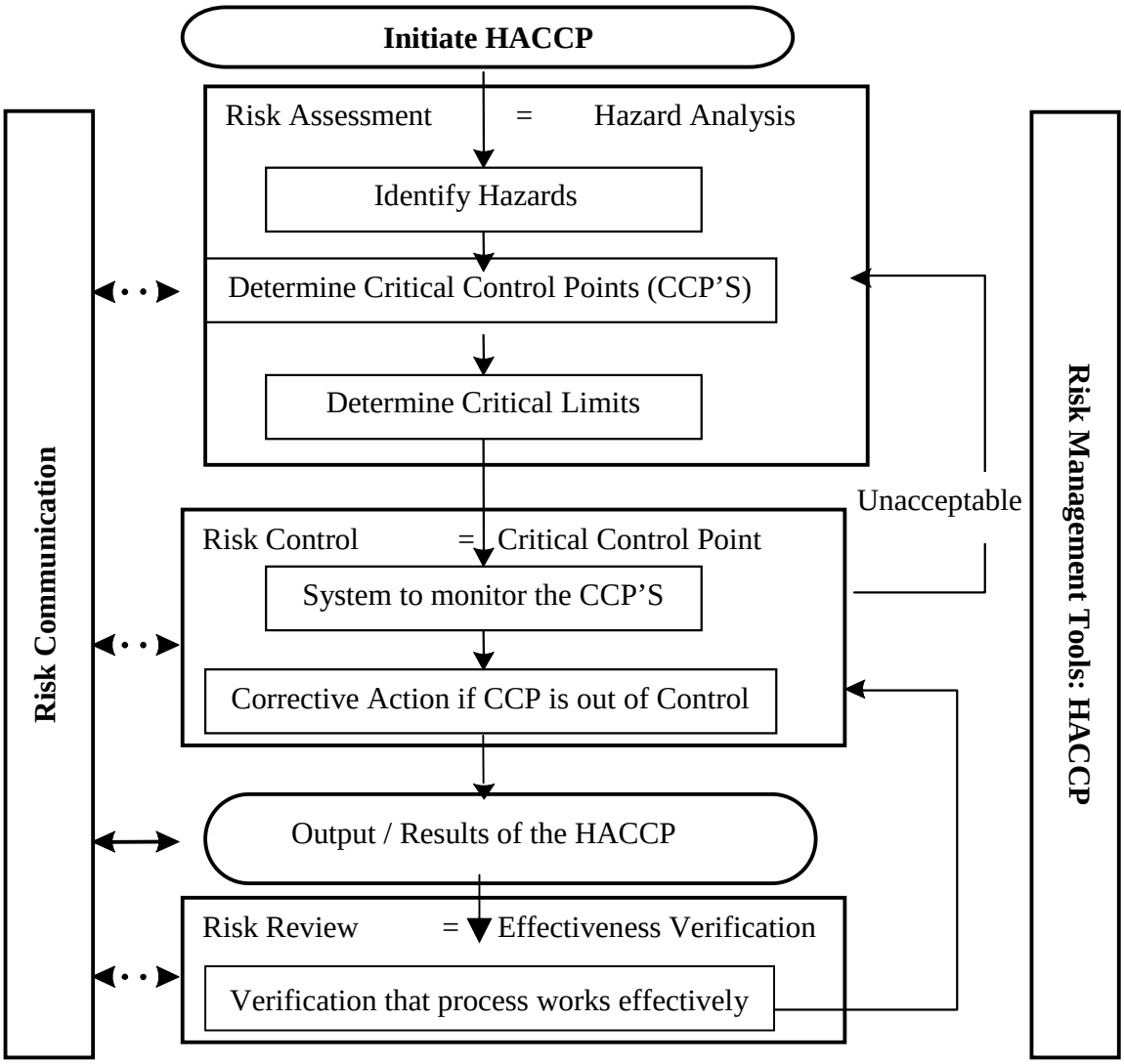
- Conduct a hazard analysis and identify preventive measures for each step of the process.
- Determine the critical control points
- Establish critical limits
- Establish a system to monitor the critical control points to reduce risk to acceptable level.
- Establish the corrective action to be taken when monitoring indicates that the critical control points are not in a state of control.
- Establish system to verify that the HACCP system is working effectively;
- Establish a record-keeping system.

Potential Areas of Use(s) are following but not limited to:

- Material receipt
- Sampling
- Analysis
- Release
- Dispensing
- Manufacturing Process
- Packaging Process
- In-process analysis
- Finished product analysis
- Finished goods storage
- Dispatch of finished product

SR. NO.	QUESTION ANSWER

The flow chart for Hazard Analysis and Critical Control Points is as follows:



Basic Risk Management Facilitation Method :

Simple techniques that are commonly used to structure risk management by gathering/ organizing data and facilitating decision making are as follows :

Flowcharts:
Pictorial presentation of a process and breaking the process down into its constituent steps.

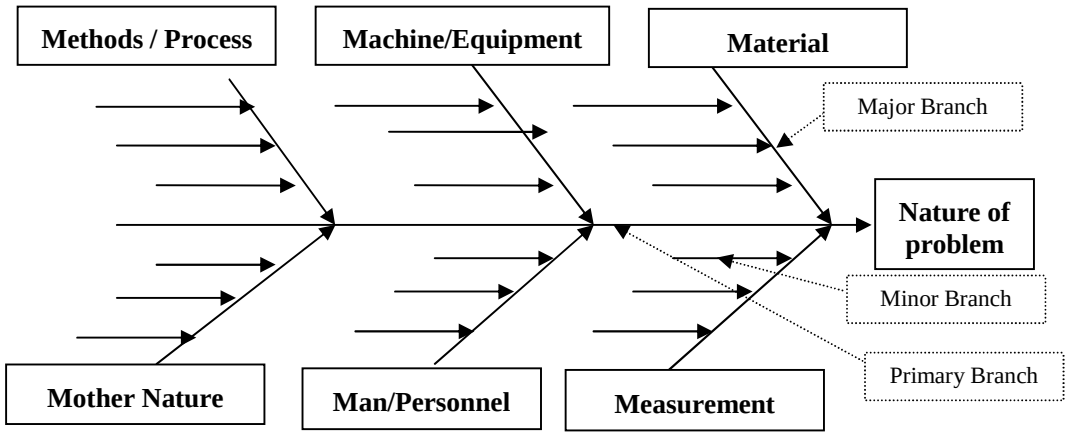
Check sheets:
Present information in an efficient format which can be accomplished with a simple listing of items.

SR. NO.	QUESTION ANSWER

Process mapping:
The indicators can be selected based on unit operations and their interrelation can be shown. Complex processes and associated risks shall be analyzed systematically.

Example: Dispensing → Sieving → Granulation → Drying → Blending → Compression → Coating → Packaging

Cause and Effect Diagram (Ishikawa / Fish Bone Diagram):
The Ishikawa/Fish Bone Diagram is used to associate multiple possible causes with single effect.



The Primary branch represents the effect, major branch corresponds the major causes and minor branch corresponds to more detailed causal factors.

SR. NO.	QUESTION ANSWER
19.0	**STABILITY STUDIES**
19.1	**DEFINATION:** **What is stability studies** The ability of a pharmaceutical product to retain its physical and chemical properties within specified limits throughout its shelf life. **TYPES OF STABILITY STUDIES** **Long term testing** Stability studies under the recommended storage condition for the re-test period or shelf life proposed (or approved) for labeling. **Intermediate testing** Studies conducted at 30°C/65% RH and designed to moderately increase the rate of chemical degradation or physical changes for a drug substance or drug product intended to be stored long term at 25°C. **Accelerated testing** Studies designed to increase the rate of chemical degradation or physical change of a drug substance or drug product by using exaggerated storage conditions as part of the formal stability studies. Data from these studies, in addition to long term stability studies, can be used to assess longer term chemical effects at non-accelerated conditions and to evaluate the effect of short term excursions outside the label storage conditions such as might occur during shipping. Results from accelerated testing studies are not always predictive of physical changes. **Climatic zones** The four zones in the world that are distinguished by their characteristic prevalent annual climatic conditions.

Climatic Zone No.	Definition	Storage Condition	Areas covered under the zone
I	Temperate climate	21°C & 45% RH.	United Kingdom, Northern Europe, Canada, Russia, United states, Japan etc.
II	Subtropical and Mediterranean climate	25°C/60% RH	United States, Japan, Southern Europe (Portugal-Greece) etc.
III	Hot & dry climate	30°C/35% RH	Australia, Argentina, Egypt, Iran, Iraq, Sudan, India etc.
IVA	Hot & humid climate	30°C/65%	Brazil, Ghana, Indonesia, Nicaragua, Srilanka, Vietnam, Philippines, Uganda, Thailand, India etc.
IVB	Hot & very humid climate	30°C/75%	Brazil, Asian countries etc.

SR. NO.	QUESTION ANSWER

Factors affecting stability of the product

Temperature:
The rate of chemical reaction increases exponentially for each 10°C increase in temperature. This relationship has been observed for nearly all drug hydrolysis and some drug oxidation reaction.

Light:
Exposure to primarily, UV illumination may cause oxidation (photo oxidation) and scission (Photolysis) of covalent bonds.

Air:
Presence of oxygen, nitrogen.

Humidity (Moisture):
Esters & beta-lactoms are the chemical bonds that are most likely to hydrolyze in the presence of water. E.g. the acetyl ester in aspirin is hydrolyzed to acetic acid and salicylic acid in the presence of moisture, but in a dry environment the hydrolysis of aspirin is negligible.

Selection of Batches
For new drug product, samples of at least three consecutive validation batches shall be kept for accelerated and long-term stability.

For routine stability study, one commercial batch shall be kept for long term stability on every year.

Testing frequency
Testing frequency shall be determined based on condition at which stability is performed.

Accelerated
Accelerated stability shall be conducted at 0,1,2,3 and 6 months.

Long term
Long-term stability studies shall be carried out at the intervals of,

Every three months on first year 0, 3, 6,9,12,
Every six months on second year 12, 18, 24
Every year thereafter through the proposed shelf life 24, 36, 48 and 60
Eg: 0, 3,6,9,12,18,24,36,48 and 60 months.

Intermediate

Intermediate stability studies (minimum four time points, including initial and final points) shall be carried out at 0,3,6,9 and 12 months or up to 60 months.

SR. NO.	QUESTION ANSWER

Sampling for Stability Study

QA shall inform to QC regarding type of stability study to be performed.

QC shall calculate the sample quantity and shall inform to QA.

Total sample quantity per batch shall be equivalent to 1.5 times of the quantity required for single complete or partial analysis & based on number of stations plus additional one station (since stability testing has to be continued for 12 month beyond the expiry).

Incubation of Stability Samples and Storage conditions

Samples shall be incubated as per below guideline.

Identify the storage conditions based on the Pharmacopoeial data or literature information or R&D information. For add on batch use long term storage conditions.

The long term testing shall cover a minimum of 12 months' duration on at least three validation batches at the time of submission and shall be continued for a period of time sufficient to cover the proposed shelf life.

Long term, accelerated, and, where appropriate, intermediate storage conditions for drug products are detailed in the sections below.

Study	Storage condition	Minimum time period covered by data at submission
Long term	25°C ± 2°C / 60% RH ± 5% RH or 30°C ± 2°C / 65% RH ± 5% RH	12 months
Intermediate*	30°C ± 2°C / 65% RH ± 5% RH	6 months
Accelerated	40°C ± 2°C / 75% RH ± 5% RH	6 months

* If 30°C ± 2°C / 65% RH ± 5% RH is the long-term condition, there is no intermediate condition.

If long-term studies are conducted at 25°C ± 2°C/60% RH ± 5% RH and "significant change" occurs at any time during 6 months' testing at the accelerated storage condition, additional testing at the intermediate storage condition should be conducted and evaluated against significant change criteria. The initial application should include a minimum of 6 months' data from a 12-month study at the intermediate storage condition.

Temperature & Humidity of stability incubator shall be monitored on daily basis. If incubation of the stability samples is delayed by 30 days or more from the release date of the batch, initial (0 month) analysis shall be performed again before incubation.

SR. NO.	QUESTION ANSWER

Analysis of the sample shall be performed on the due date or if not possible, then complete within below tolerance limit from due date.

Sr. No.	Stability Station	Tolerance (From due date of analysis)
1.	1M , 2M, 3M Accelerated, 3M long term, 3M Intermediate term	± 07 days
2.	6M Accelerated 6M, 9M, 12M long term. 6M, 9M, 12M Intermediate term.	± 15 days
3.	18M & onwards of long term.	± 30 days

If there is any out of trend result or failure to meet specification (significant change) in stability analysis, results shall be intimated to Head – QC.

Head – QC or designee shall investigate the out of trend (OOT) results according to the SOP No. QAD 087 of OOT.

In case of Changes in the manufacturing process or site:
If minor changes done in the manufacturing process, Sample from batches produced under each change shall be added to stability program (one batch).

If major changes done in the manufacturing process, collect the samples from the new batches (three batches) and perform the stability like new product. In such a case the protocol and report procedure number shall be changed.

In case of manufacturing site change, evaluate the affect on stability of the drug product by keeping one batch for stability.

Which guideline

ICH guideline: ICH Q1A (R2)
Orange guide

SR. NO.	QUESTION ANSWER
20.0	**ANALYTICAL METHOD VALIDATION**
20.1	**DEFINATION:** **Analytical Method Validation:** Validation of an analytical procedure is the process by which it is established, by laboratory studies, that the performance characteristics of the procedure meet the requirements for the intended analytical applications. **Specificity:** Ability to assess unequivocally the analyte in the presence of components which may be expected to be present (impurities, degradants, matrix). It is a measure of the degree of interference from such things as other active ingredients, excipients, impurities, and degradation products, ensuring that a peak response is due to a single component only. **Precision:** The precision of an analytical procedure expresses the closeness of agreement (degree of scatter) between a series of measurements obtained from multiple sampling of the same homogeneous sample under the prescribed conditions. Precision may be considered at three levels: repeatability, intermediate precision and reproducibility. **Repeatability** (Method Precision): Repeatability expresses the precision under the same operating conditions over a short interval of time. Repeatability is also termed intra-assay precision. **Intermediate precision (Ruggedness):** Intermediate precision expresses within-laboratories variations: different days, different analysts, different equipment, etc. **Accuracy:** The accuracy of an analytical procedure expresses the closeness of agreement between the value which is accepted either as a conventional true value or an accepted reference value and the value found. **Linearity:** The linearity of an analytical procedure is its ability (within a given range) to obtain test results which are directly proportional to the concentration (amount) of analyte in the sample. **Range:** The range of an analytical procedure is the interval between the upper and lower concentration (amounts) of analyte in the sample (including these concentrations) for which it has been demonstrated that the analytical procedure has a suitable level of precision, accuracy and linearity. **Detection Limit (DL):** The detection limit of an individual analytical procedure is the lowest amount of analyte in a sample which can be detected but not necessarily quantitated as an exact value.

SR. NO.	QUESTION ANSWER

Quantitation Limit (QL):

The quantitation limit of an individual analytical procedure is the lowest amount of analyte in a sample which can be quantitatively determined with suitable precision and accuracy. The quantitation limit is a parameter of quantitative assays for low levels of compounds in sample matrices, and is used particularly for the determination of impurities and/or degradation products.

Robustness:

The robustness of an analytical procedure is a measure of its capacity to remain unaffected by small, but deliberate variations in method parameters and provides an indication of its reliability during normal usage.

PROCEDURE

The typical process that is followed in an analytical method validation is chronologically listed below,

- Planning and deciding on the method validation experiments
- Preparation and approval of method validation protocol
- Execution of the method validation activity
- Reporting the analytical method validation.
- Finalizing the analytical method.

Analytical methods to be revalidated in following circumstances;

- Changes in the composition of a finished product (Drug product).
- Changes in the Analytical method.
- During the optimization of the drug product process, significant changes were introduced into the process. To ensure that the analytical method will still be able to analyze the potentially different profile of the drug product, revalidation may be necessary.
- The degree of revalidation required depends on the nature of the changes. Certain other changes may require validation as well.

Types of analytical procedure to be validated,

- **Category I :** Limit test of the active moiety in samples of drug substance or drug product or other selected component (s) in the product.
- **Category II:** Quantitative tests for impurities content and Limit tests for the control of impurities;
- **Category III:** Determination of performance characteristic (e.g. Dissolution, drug release)
- **Category IV:** Identification Test

SR. NO.	QUESTION ANSWER

Analytical performance parameters	Requirement				
	Category I	**Category II**		**Category III**	**Category IV**
	Assay	Testing for Impurities		Dissolution, drug release	Identification test
		Quantitation	Limit Tests		
Accuracy	Yes / #	Yes / #	No	Yes / #	No
Precision -System precision - Repeatability - Intermediate Precision	Yes	Yes	No	Yes	No
Specificity	Yes / #	Yes / #	Yes	Yes / #	Yes
Detection limit	No	No*	Yes	No	No
Quantitation limit	No	Yes	No	No	No
Linearity	Yes	Yes	No	Yes	No
Range	Yes	Yes	No	Yes	No
Robustness	Yes	Yes	No	Yes	No
Stability study of analytical solution	Yes / #	Yes / #	No	Yes / #	No
* May be required, depending on the nature of the specific test. # To be performed if the analytical procedure is compendial (Pharmacopoeial)					

SPECIFICITY/SELECTIVITY

For identification test

Analyze the finished product sample along with reference standard or certified working standard or reference material and analyze the finished product sample which do not containing the analyte (Placebo), compare the results.

For assay and impurity tests

- For chromatographic procedure the specificity shall be demonstrated by resolution of the two closest eluting compounds and their peak purity and blank determination.
- For non-chromatographic procedure (e.g. titration) combination of assay and a suitable test for impurities can be used.
- Spike the finished product or drug substance with impurities and/or excipients as per specification level and analyze it along with unspiked finished product or drug substance.
- Check that the all the spiked components are resolved from each other according to the acceptance criteria.

Acceptance criteria:

- System suitability should pass.
- No interfering peaks shall be eluted at the retention time of analyte.
- The resolution between analyte peak and any closely eluting peak should be more than 2.0.
- The peak purity due to analyte should not be less then 990 or 0.99 whichever is applicable.

SR. NO.	QUESTION ANSWER

PRECISION
Precision is measured as the percent relative standard deviation (% RSD) for significant number of samples.

System precision:
Carry out minimum 5 determinations of standard /reference solution at 100% of test concentration (concentration of compound of interest given in analytical method).

Acceptance criteria: The relative standard deviation of five replicate injections of standard/reference solution should not be more than 2.0%.

Repeatability (Method precision):
For Assay/Related substances: Prepare 6 different sample preparations as per concentration of compound of interest given in analytical method from a sample of one batch and determine the results from these six-sample preparation.

Acceptance criteria:

% of Analyte in Sample	% RSD
0.001 to 2 %	Should not be more than 10 %.
More than 2 % to 10 %	should not be more than 5 %
More than 10 % to 100 %	should not be more than 2 %

For Dissolution: Prepare 2 sets of 6 units as per concentration of compound of interest given in analytical method from a sample of one batch and determine the results from 12 units preparation

Acceptance criteria: Over all % RSD of % release of two sets should not be more than 6.0 %.
Intermediate precision:

For Assay / Related substances: Analyze the sample of single batch six times by different analysts on different days using different instrument and where applicable use different column or electrode.

Acceptance criteria: The % RSD of results of two different sets (method precision and intermediate precision) should be as per shown in below table.

% of Analyte in Sample	% RSD
0.001 to 2 %	Should not be more than 10 %.
More than 2 % to 10 %	should not be more than 5 %
More than 10 % to 100 %	should not be more than 2 %

For Dissolution: Analyze the sample of single batch (6 units) two times by different analysts on different days using different instrument.

SR. NO.	QUESTION ANSWER

Acceptance criteria: % RSD of results of two different sets (method precision and intermediate precision) should not be more than 6.0 %.

ACCURACY

For the assay of the finished product:

Analyze the synthetic mixtures of finished product components (placebo) spiked with known quantities of drug substance to be analyzed.

Prepare the sample in the range of 80,100,120% of label claim and analyze it in triplicate at each concentration.

If it is not possible to prepare placebo due to non-availability of other components then add known quantities of analyte to the finished product. (4.1.2 b of ICH Q2 (R1))

Accuracy may be inferred once precision, linearity and specificity have been established.

For impurities test (quantitation):

Analyze the finished product sample spiked with known amounts of impurities at the specification level.

Prepare the sample in the range of 80%, 100%, and 120% of specification level and analyze it in triplicate at each concentration.

For dissolution: Add known amount of standard to that of placebo (above and below the nominal level) at 3 different levels i.e. 70%, 100% and 130% to cover both above and below the nominal levels.
Calculate the data as % of label claim, mean and % RSD at each concentration.
Report the data as the percent recovery by the assay of the known added amount of analyte in the sample or as the difference between the mean and the accepted true value together with confidence intervals.

Acceptance criteria: For Assay / Related substances

- System suitability should pass.
- Recovery should not less than 90.0 %.
- For % RSD of recovery for all levels,

% of Analyte in Sample	% RSD
0.001 to 2 %	Should not be more than 10 %.
More than 2 % to 10 %	should not be more than 5 %
More than 10 % to 100 %	should not be more than 2 %

Acceptance criteria: Dissolution

- Recovery at each level should in between 95.0% to 105.0%.
- % RSD for the recovery of all the levels should not be more than 5.0%.

SR. NO.	QUESTION ANSWER

LINEARITY AND RANGE:
Linearity should be evaluated by visual inspection of a plot of signals as a function of analyte concentration or content.

The below table details the methodology to perform linearity and range parameter.

Type of method	Minimum concentration to be prepared	Range
Assay	7	10, 30, 50, 80, 100, 120 & 200 % of the test concentration.
Content uniformity	5	70 to 130 % of the test concentration.
Dissolution testing	5	± 20 % of the specified range.
Impurity	5	From quantitation limit to 120% of specification
Assay & impurity are performed together as one test	5	From quantitation limit to 120% of the assay specification.

Demonstrate the linearity by the use of correlation coefficient, y- intercept, and slope of the regression line.

Acceptance criteria:
The correlation coefficient should not be less than 0.99 for Assay method and for impurity quantification method the correlation coefficient should not be less than 0.98.

LIMIT OF DETECTION (applicable only for impurity methods):
It is a limit test that specifies whether or not an analyte is above or below certain value which can not be quantified as an exact value.

Based on Visual Evaluation
Measurement by visual evaluation for non-instrumental methods (e.g. TLC/titration);

Determined the detection limit by the analysis of samples with known concentrations of analyte.

Prepare a sample at lowest concentration of analyte and establish the minimum level at which the analyte can be consistently detected.

Based on Signal-to-Noise:
Measurement by signal to noise ratio for instruments which exhibit baseline noise;

Determine the signal-to-noise ratio by comparing measured signals from samples with known lowest concentrations of analyte with those of blank samples and establish the minimum concentration at which the analyte can be consistently detected. And measure the signal-to-noise ratio.
Acceptance Criteria: A signal-to-noise ratio between 2:1 or 3:1 is required.

SR. NO.	QUESTION ANSWER

Based on the Standard Deviation of the Response and the Slope:

Determine the slope of calibration curve by analyzing the samples at different concentration in the range of detection limit.

$$\text{Detection Limit (DL)} = \frac{3.3 \times \text{Standard deviation (SD) of response}}{\text{Slope of calibration curve}}$$

LIMIT OF QUANTITATION (applicable only for impurity methods):

Based on Visual Evaluation:

Measurement by visual evaluation for non-instrumental methods (e.g. TLC/titration);

Determined the quantitation limit by the analysis of samples with known concentrations of analyte.

Prepare a sample at lowest concentration of analyte and establish minimum level at which analyte can be quantified with acceptable accuracy and precision.

Based on Signal-to-Noise:

Measurement by signal to noise ratio for instruments which exhibit baseline noise;

Analyze minimum 6-sample solution at decreasing concentration in the expected range of quantitation limit.

Determine the signal-to-noise ratio by comparing measured signals from samples with known lowest concentrations of analyte with those of blank samples and establish the minimum concentration at which the analyte can be consistently quantified. And measure the signal-to-noise ratio.

Acceptance criteria: A signal to noise ratio 10:1 is required.

Based on the Standard Deviation of the Response and the Slope:

Determine the slope of calibration curve by analyzing the samples at different concentration in the range of quantitation limit.

$$\text{Quantitation Limit (QL)} = \frac{10 \times \text{Standard deviation (SD) of response}}{\text{Slope of calibration curve}}$$

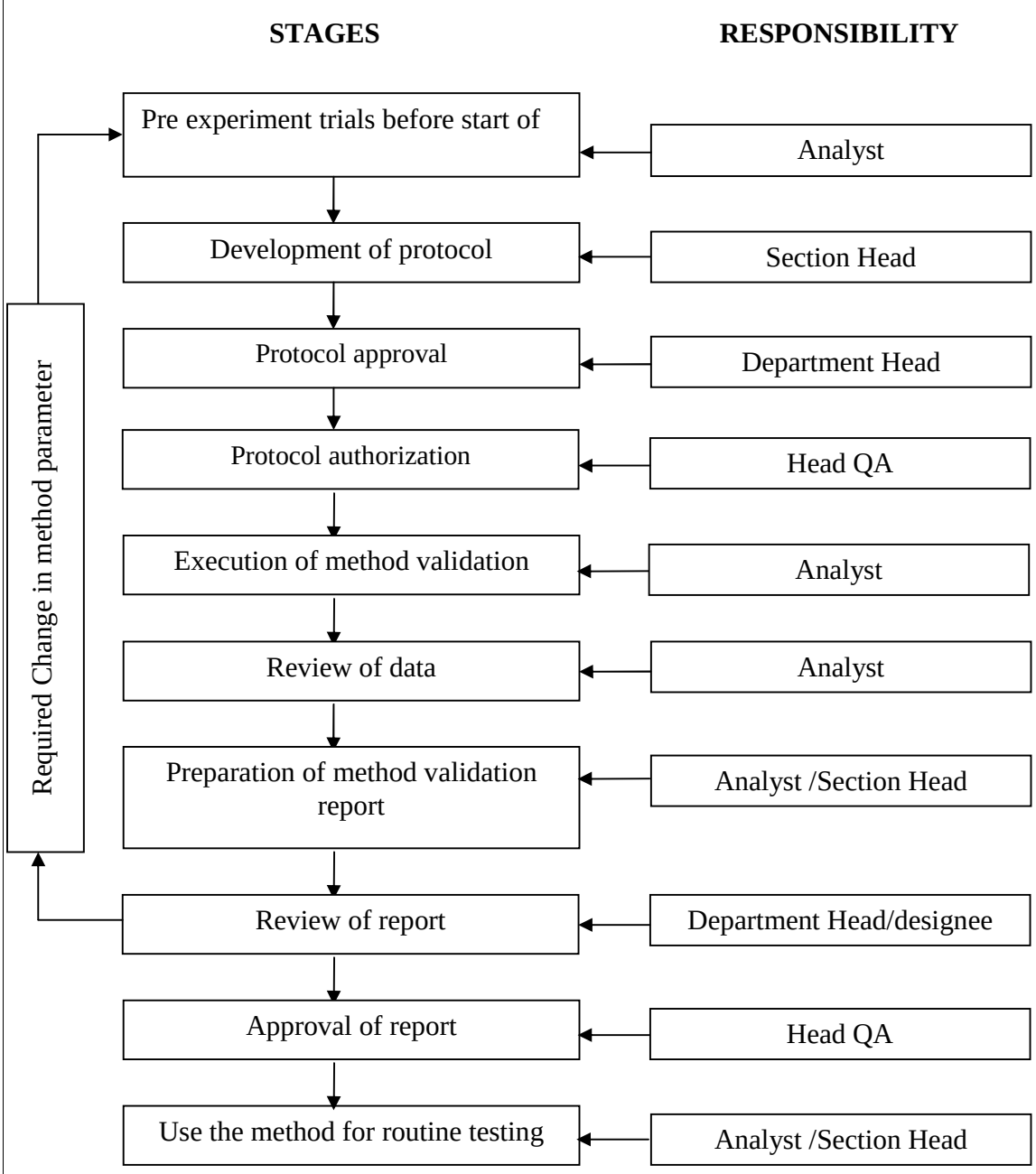
Precision at Quantitation Limit (QL):

Prepare a sample solution at the QL concentration determined by adapting any of above method and analyze it for six times and measured the precision (%RSD) at this concentration.

The acceptance criteria for precision shall be complied the requirement given under acceptance criteria of precision point no.5.9.3.2.

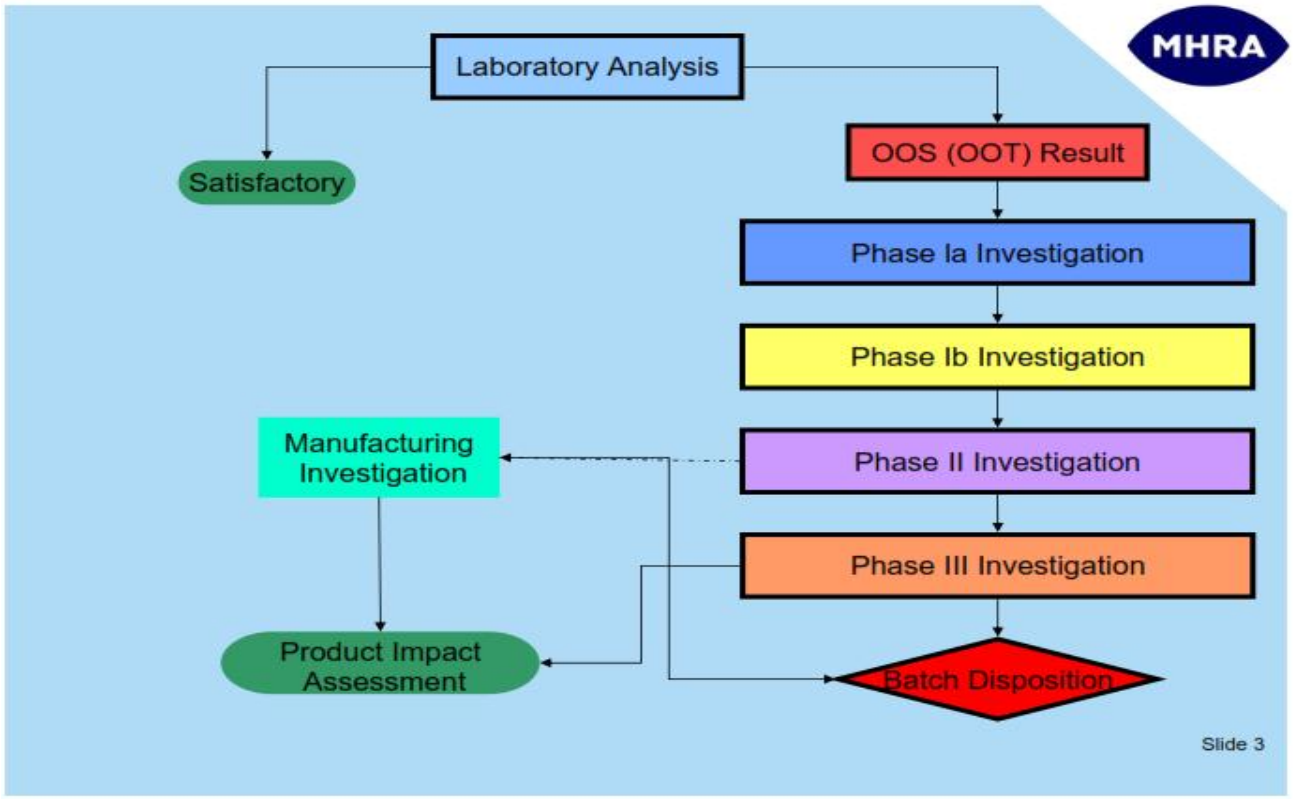
SR. NO.	QUESTION ANSWER
	ROBUSTNESS: The robustness of the method shall be performed by varying some or all conditions given below; • By changing pH of buffer/ mobile phase by ± 0.2. • By changing the flow rate by ± 50% • By changing the organic phase of mobile phase composition ± 30 % relative but can not be exceed 10% absolute or 2 % absolute. • By changing the columns (Different lots and/or suppliers) • By changing the column oven temperature by ±10°C • By changing the extraction time (if applicable) Analyze the sample solution for each condition and compare the data with the data of method precision **Acceptance criteria:** • The system suitability should pass for each variation. • The overall % RSD (with method precision) should not be more than 2.0 for assay, 5.0 for dissolution and 10.0 for individual experiment of impurities. **STABILITY STUDY OF ANALYTICAL SOLUTION**: Stability study of analytical solution shall be performed for at least 24 hours for chromatographic assay and impurity tests, addition time interval can be extended. **For assay & dissolution**, prepare the standard (where applicable) and sample solution according to the proposed method, analyzes initially and at different time interval and find out the cumulative %RSD. **Acceptance criteria:** The cumulative %RSD should not be more than 2.0. For impurity test, spike the sample solution with known amount of impurities, analyze it initially and different time intervals and find out the cumulative %RSD. **Acceptance criteria:** a. The cumulative %RSD should not be more than 10.0. b. No new peak should elute. When measurements are susceptible to variations in analytical conditions, the analytical conditions should be suitably controlled or a precautionary statement should be included in the procedure **System suitability testing** System suitability parameters are to be followed as given in STP. **After the laboratory work** After completion of the laboratory work and documentation of the data, QC-officer shall review the complete data for correctness of calculation and methodology.

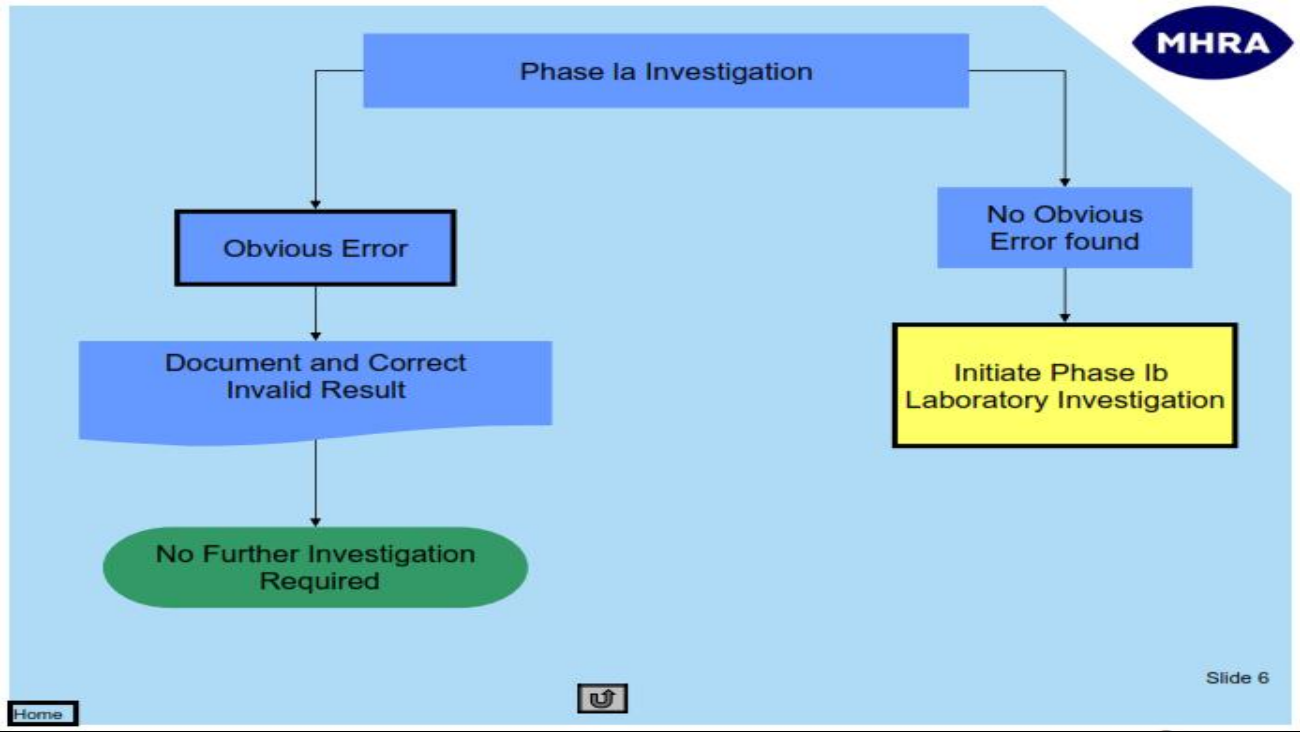
SR. NO.	QUESTION ANSWER



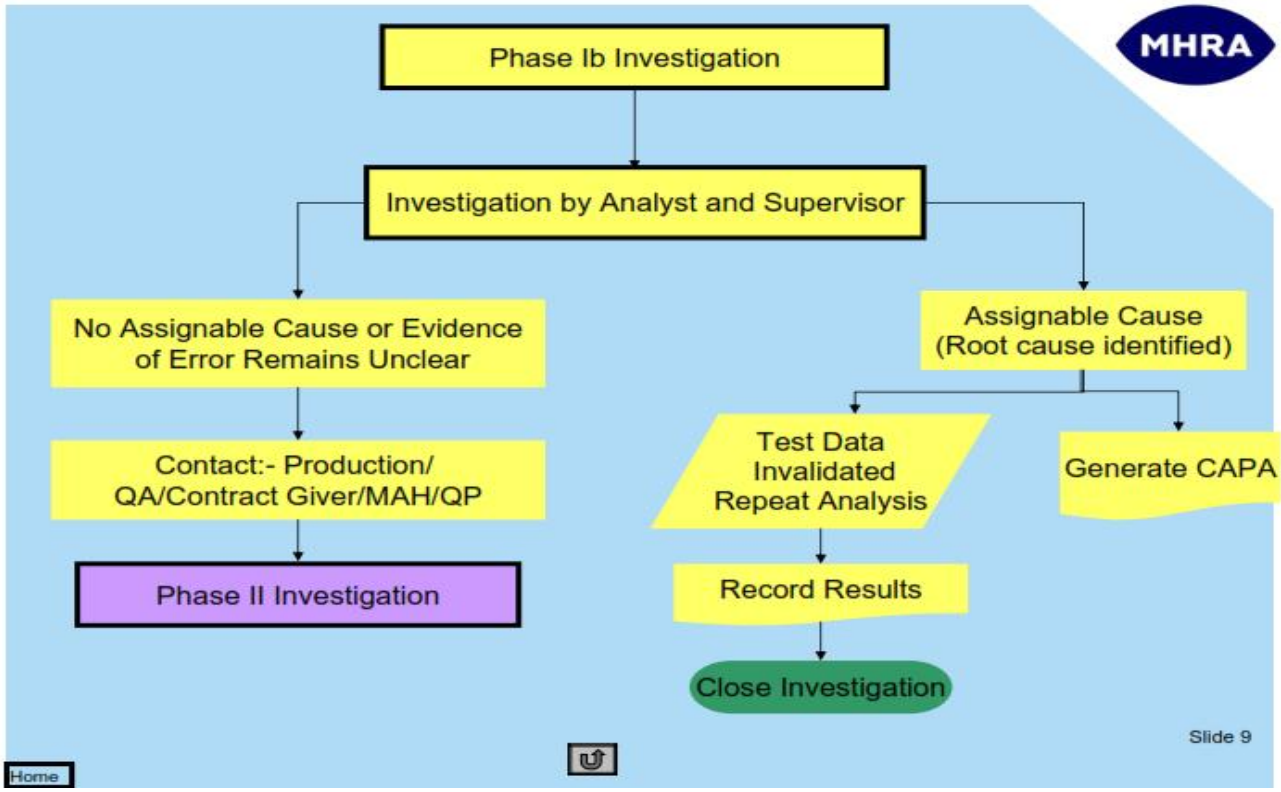
SR. NO.	QUESTION ANSWER
21.0	**OUT OF SPECIFICATION**
21.1	**DEFINATION :** **Out Of Specification (OOS) results:** Test results that does not comply with the pre-determined acceptance criteria (e.g. filed application, approved marketing submission, official compendia or internal acceptance criteria). Test results that fall outside of established acceptance criteria which have been established in official compendial and/or by company documentation (i.e. raw material specification, In process/final product testing etc). **PROCEDURE :** After completion of analysis, analyst must check the data and results for compliance with specifications, When any out of specification results observed in laboratory and if no obvious explanation exists, then follow as mentioned below; • Do not discard the Standard and Test Preparations • Retain all Glassware and Sample • Check the analytical raw data sheet and chromatogram • Check the whole analysis for compliance (Self-check) Based on the request of section incharge of QC, QA person shall enter the details of out of specification in OOS log (Annexure-II) and issue the OOS investigation report (Annexure-I) QC for investigation. Incase OOS is logged, where necessary, QA shall inform to respective QP's/ MA Holder/ Regulatory bodies within 3 working days and customers based on technical agreements after the OOS is logged. After completion of OOS investigation, the same shall be communicated to respective QP's / MA Holder/ Regulatory bodies and Customers based on technical agreements. **Handling OOS results during Stability Studies** During stability study any adverse change or OOS observed and confirmed in physical or chemical parameters shall be brought to the attention of Head- QA, Manufacturing, RA, R&D. Head-QA shall do investigation on the affected batch along with all other batches manufactured at the same time period and same shall be communicated to concern regulatory agencies through Head RA. If OOS found valid for stability samples, the stability study shall be continued for testing samples of further stations. If the result of the next station sample is also found to be failing with respect to the test for which OOS was reported, the stability study shall be discontinued.

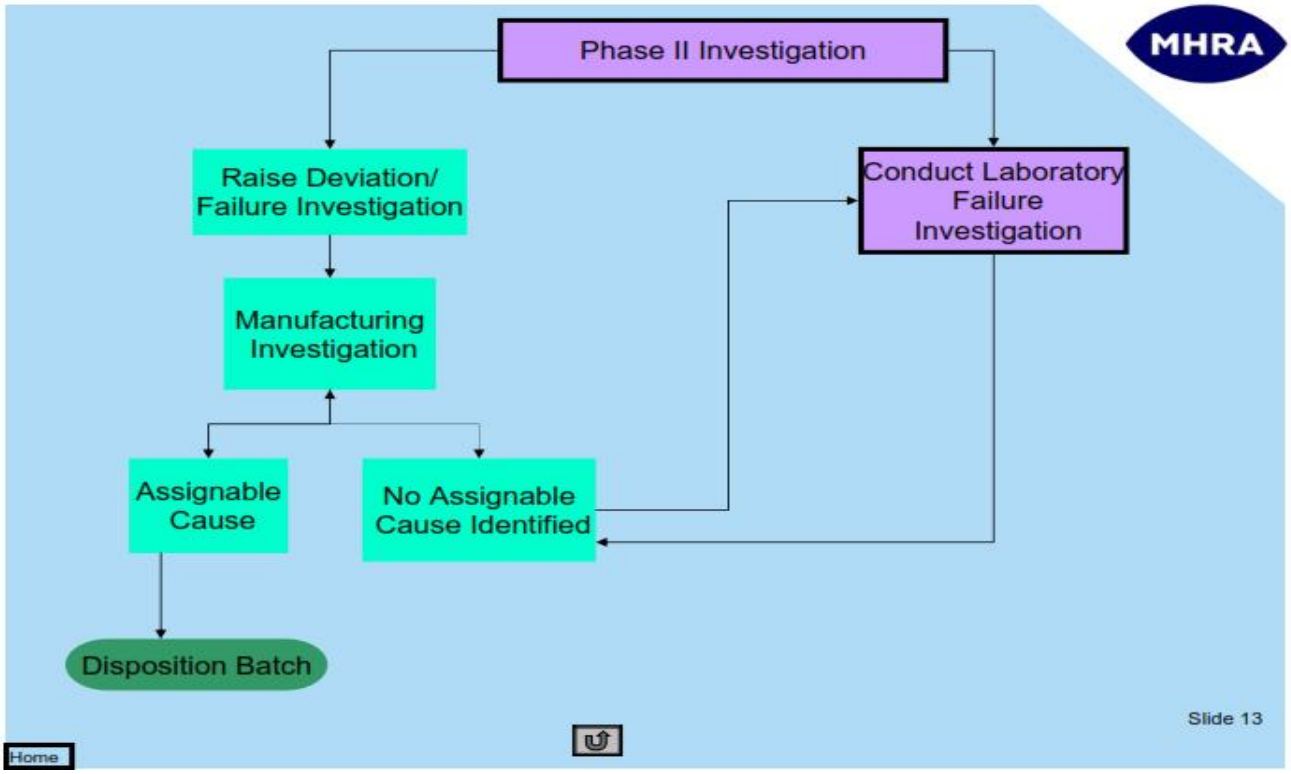
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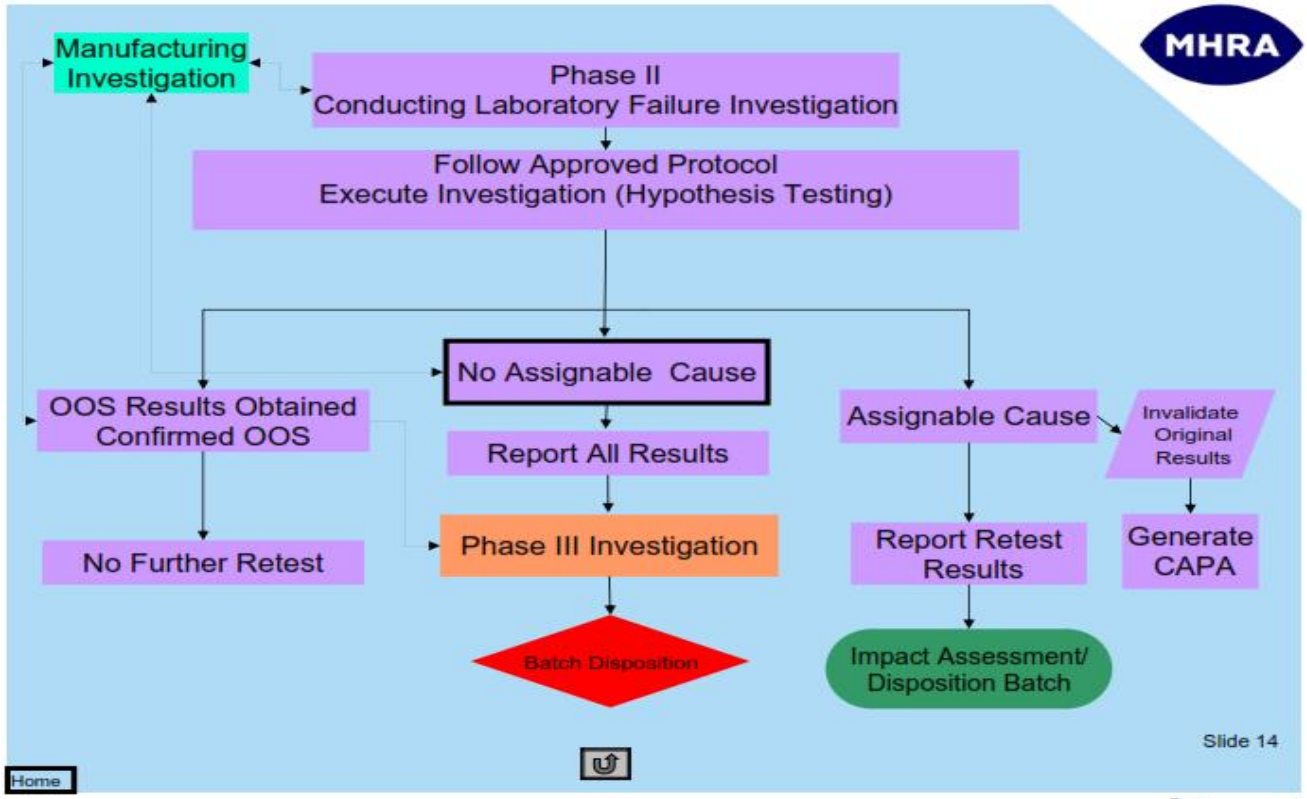


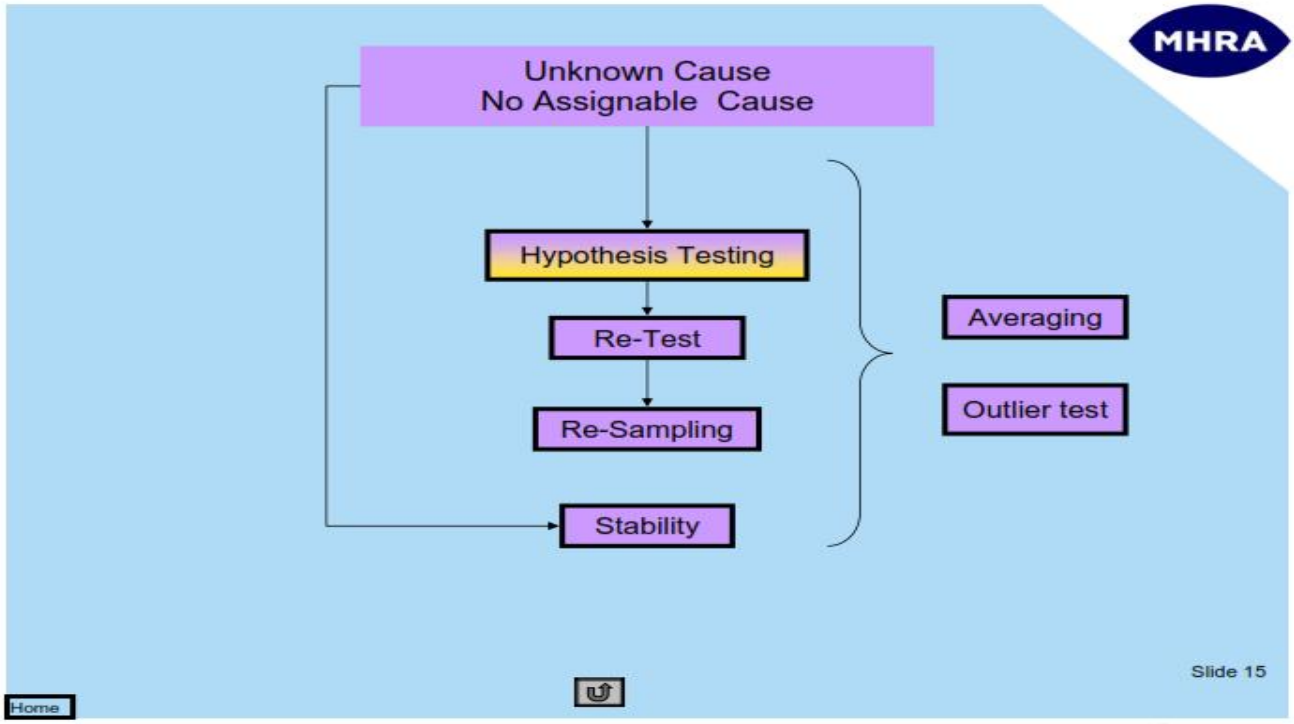
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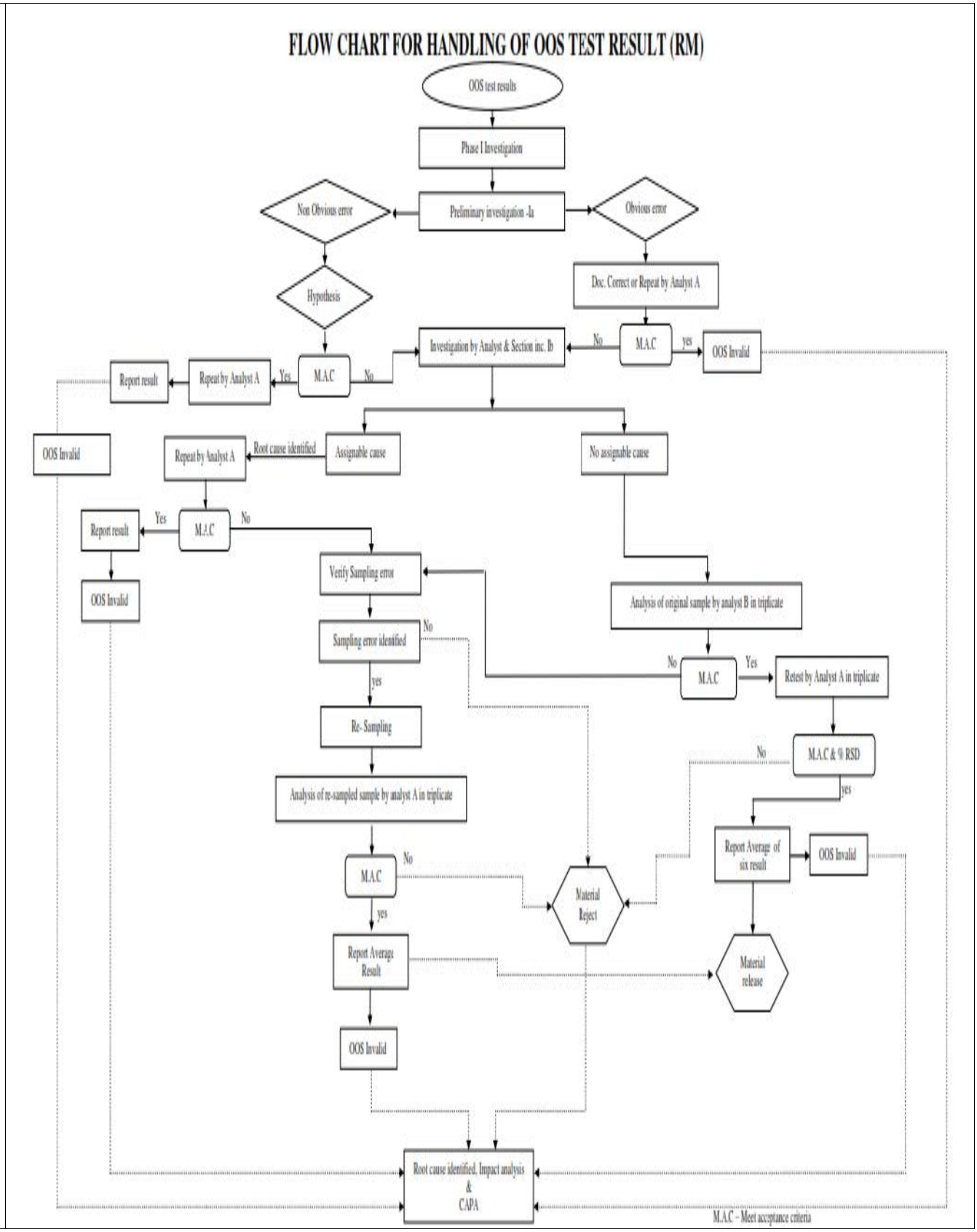


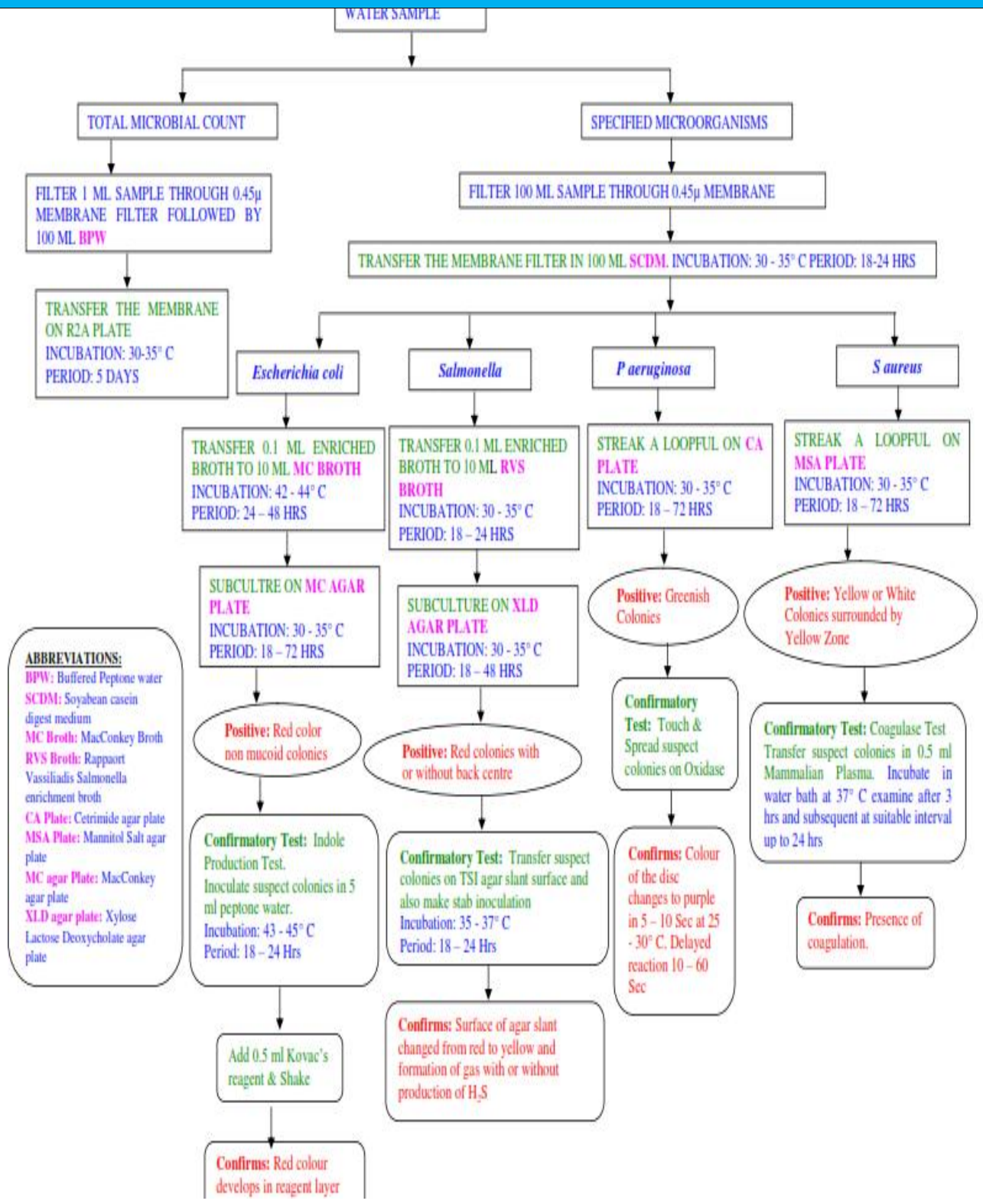
SR. NO.	QUESTION ANSWER





SR. NO.	QUESTION ANSWER



SR. NO.	QUESTION ANSWER
22.0	MICRO
22.1	

SR. NO.	QUESTION ANSWER
	The prepared plates of Soyabean casein digest agar are pre-incubated at 30°C to 35°C for 24 hours. The prepared plates of Sabouraud Chloramphenicol Agar are pre-incubated at 20°C to 25°C for 24 hours. Active Air sampling by Air sampling Passive Air sampling by settle plate **Active Air sampling by Air sampler** • Autoclave the sampling head of the Air-Sampler by covering it with aluminum foil or hydrophobic paper. • Mark each plate with Date of Exposure, Name of Location or Location No. • Keep all the SCDA plate, 70% IPA & hand gloves in sampling box • Enter in the respective areas by following the proper entry (gowning) procedure. • Open the sterile media plate and place it in the sampler subsequently by placing sterile sampling head of the Air-sampler over the media plate. • Sample 1000 liters of air from a designated sampling point refer Annexure-XII • During sequential sampling; disinfect the air sampling head with filtered 70% IPA. • After sampling open the head of Air –sampler and take out the agar plate from the sampler. • Cover the plate with lid immediately and put it into the sampling box. • Exit from respective area by following the exit procedure. • Incubate the exposed plate in an inverted position in the BOD incubator at 20-25°C for 72 hrs followed by 30-35°C for 48 hrs. • Control test: Keep same lot of unexposed media plate in BOD Incubator with exposed plate as a negative control. • After incubation record the observations in respective Annexure. • Connect the Air sampler in “ON” mode with PC through data cable. **Passive Air sampling by settle plate** • Mark each plate with Date of Exposure, Name of Location or Location No. • Keep all the SCDA & SCA plate, 70% IPA & hand gloves in sampling box • Enter in the respective areas by following the proper entry (gowning) procedure. • Place the marked Soyabean casein digest agar and Sabouraud Chloramphenicol Agar Plates to its respective location as per annexure-I. • Open the lid of the plate, keep the lid supported with edge in such a way that the lid Should placed at slight vertical position. • Expose the plates in designated areas for 4 hours. • At the end of exposure time, close the plates and transfer to the SS petriplates container. • Exit from respective area by following the exit procedure. • Transfer the plates to microbiology laboratory. • Incubate the exposed Sabouraud Chloramphenicol agar plates in BOD Incubator at 20°C to 25°C for 5 days and Incubate the soyabean casein digest agar plates at 30°C to 35 °C for 48 hours. • Control test: Keep same lot of unexposed media plate in BOD Incubator with exposed plate as a negative control • Record the total no. of colony forming unit (cfu) observed after the completion of 48 hours and 5 days of incubation in respective Annexure – III, IV and V.

SR. NO.	QUESTION ANSWER

- Contaminant shall be identified from its colony morphological characteristics if required, gram staining shall be carried out to differentiate Gram positive from Gram negative organism as per the SOP No. QCG 151.
- Before start the plate exposure ensure the cleaning, sanitization, AHU operation and activity of the area.

If results of microbiological environmental monitoring obtained out of alert limit, Microbiologist should inform to Head Microbiology, Quality Control & Head QA or his designee.
Start the Out Of limit (OOL) investigation

Acceptance criteria
Limits for settle plate of Manufacturing Area, Sampling Area, Dispensing Area and Packing Hall.

Plates	Alert Limit	Action Limit
Total Bacterial Count	NMT 60 cfu / plate	NMT 100 cfu / plate
Total Fungal Count	< 1 cfu / plate	< 1 cfu / plate

Limits for settle plate of RLAF in Sampling and Dispensing Area

Plates	Alert Limit	Action Limit
Total Bacterial Count	< 1 cfu / plate	< 1 cfu / plate
Total Fungal Count	< 1 cfu / plate	< 1 cfu / plate

Limits for Air sampling of Manufacturing Area, Sampling Area, Dispensing Area and Packing Hall.

Plates	Maximum Allowable Limit cfu / M^3
Total Bacterial Count	NMT 200 cfu / M^3
Total Fungal Count	< 1 cfu / M^3

Limits for Air sampling of RLAF in Sampling and Dispensing Area

Plates	Maximum Allowable Limit cfu / M^3
Total Bacterial Count	< 1 cfu / M^3
Total Fungal Count	< 1 cfu / M^3

Limit for Surface Monitoring of Reverse Laminar Air Flow (RLAF)

Plates	Maximum Allowable Limit cfu / contact plate
Total Bacterial Count	NMT 3 cfu / contact plate (Including Floor)
Total Fungal Count	< 1 cfu / contact plate

Frequency
For Settle Plate: Once in a Month (Every first week of the month cover all the sampling point)
For Air sampling: Twice in a Month (Fortnightly)
For Surface Monitoring: Once in a Month.

SR. NO.	QUESTION ANSWER
23.0	**TRAINING**
23.1	**DEFINATION:** Training is a process of teaching or learning a skill through instructions. **INDUCTION TRAINING** The induction training shall be given based on induction manual by Head Personnel & Administration or his designee about the company, HR rules / policies, organization structure, various department & their functioning, EHS policies, etc. **ON JOB SOP TRAINING** On satisfactory completion of induction training new employee shall fill his / her detail in signature log (e.g. name, date of joining, designation, full signature and short signature (initials) in the specimen signature log. The New employee shall read and understand the SOP of his department as per training matrix (Annexure-III) and fill in the "Training record of SOP" as per Annexure-IV. If there is any query regarding any SOP, it shall be explained or clarified by department head / designee. After understanding of the entire SOP, the department head shall sign the Annexure – IV and introduce the new employee to the section head where he / she will work. The section head shall identify the task/work for where he / she will work. And accordingly, the new employee shall perform the task by himself / herself in presence of section head. The evaluation should be done by question or answer on relevant topic. Acceptance criteria for the assessment of training are specified under the section of Training assessment criteria. After completion of the on job training, if the performance of the new employee found satisfactory, then work authorization certificate shall be issued to the new employee for the activity by section head and HOD and it is filed in his/her respective training file. Refer Annexure-V. Exemption should consider in case of HOD or higher position where on job training is not required **cGMP TRAINING PROGRAM** cGMP training program shall be given in two mode, 1. Basic cGMP training program 2. Refresher cGMP training program **CLASS ROOM TRAINING** The training shall be conducted either as a classroom training or demonstration on the job or self learning by reading and understanding of the SOPs The training of each employee should conduct as per the Annual Training calendar The personnel who ever attended the training must update their "Employee Training Card

Simpal Baria

SR. NO.	QUESTION ANSWER
	NEED BASED TRAINING IDENTIFICATION The section head shall identify the training needs of the employees appropriate to his / her job requirements **External Training Program** The external training comprises of two elements, one where the external trainer or organization are brought into the site to conduct training **"In-Plant training"**, the other where the trainee is sent to an external course out side the facility **"Out side training"**. **GMP trainer's evaluation Program** The trainer shall be nominated by the head of the department in co-ordination with Head -QA based on at least the following but not limited to: • Educational qualification: Graduate in Pharmacy, Science or Engineering or Management. • Working Experience. • Working knowledge of GMP in National, Local, and Global legislation GMP. • Skills on preparation and delivery of training modules and Good communication. The qualification shall comprise the Medley Authorized Certificate (Refer Annexure-XI) that the person is an authorized trainer. **DOCUMENTATION:** Training Matrix (Annexure-III) shall be prepared at the end of the year for the next year. cGMP Training Planner (Annexure-VIII) shall be prepared at the end of every year for the next year.(Eg: cGMP Training planner for the year of 2013 shall be prepared on December, 2012.) Annual Training Calendar (Annexure-IX) shall be prepared at the end of every year for the next year. Check list for Authorized trainer (Annexure-XII) shall be maintained department wise. List of Authorized trainer (Annexure-XIII) shall be prepared at the end of every year for the next year maintained department wise. **Individual file:** • Work authorization certificate, Training Evaluation Report, Employee training Card. • Certificate for authorized trainer.(In case of Trainer) **P&A Department** • Induction Training schedule. • Induction Training Report.

PHARMA BOOK

SR. NO.	QUESTION ANSWER
24.0	**MEDICAL CHECKUP**
24.1	Every new recruit should under go medical examination before joining the company. Get the medical check up done for all employees once in a year through registered medical practitioners only. The general medical check-up include the following examination(s) i.e. Physical examination i.e. blood pressure, pulse rate, height, weight, physical abnormality, contagious skin disease, blood test. Chest X-ray for personnel working in production area who are directly exposed to the products and eye check-up (Power and color blindness) for personnel engaged in visual inspection of products and analysis in quality control laboratory. Employee should not report to the work if they are infected with any disease or they have any open lesions. About illness, employee should report to his/her department head. Department Head would decide about his /her continuation of the days work. Any employee remaining off the duty for more than 3 days on medical ground, he/she shall be allowed to work only after reviewing his/her Medical Fitness Certificate.
25.0	**PEST CONTROL**
25.1	Pest control shall be carried out by spraying the required concentration of pesticides Spraying shall be done all over the outside periphery of the building and at all entry points as per the lay out Pest control shall be carried out on weekly basis *(i.e. on every Friday)* FIRST AID TREATMENT : In case of exposure to skin , inhalation and ingestion, If in EYES - Immediately flush with plenty of water for at least 15 minutes. In case of redness, itching and burning sensation immediate seek medical advice. If SWALLOWED - If the patient is conscious, wash out mouth with water. Vomiting should be induced under the direction of physician. If spontaneous vomiting occurs, have victim lean forward with head down to avoid breathing in of vomit, rinse mouth and administer water. If INHALED - Remove victim to fresh air. Apply artificial respiration if breathing has ceased or shows signs of failing. Obtain medical attention. If ON SKIN - Wash material off the skin with plenty of water. If redness, itching or burning sensation develops, obtain medical attention.

SR. NO.	QUESTION ANSWER

Sr. no.	Name of pesticide and recommended concentration	Active ingredient (organo phosphates)	Used for control of	Mode of use
1.	Chlopryriphos - 20 %	Diethyl phosphorthoate	Crawling and flying insects	100m1 to 200 ml (as required) Of the concentrated Chemical be mixed with 5 Liters of Water and sprayed
2.	Cypermenthrin - 10 %	Cypermenthrin	Crawling and flying insects	
3.	Cyfluthrin – 2.45%	Beta cyfluthrin	Crawling and flying insects	
4.	Permethrin 25%	Permethrin	Crawling and flying insects	

26.0 RODENT CONTROL

26.1 Red color rectangle painted on floor / wall indicates point where rodent trap boxes shall be placed. The Rodent trap box point shall be numbered as RB XX where RB= Rodent trap box, XX= serial number starting from "01"

Rodent control trap box will be placed as per layout.

House keeping Supervisor / Asst. Security Supervisor / Supervisor shall check the entire rodent trap for any Rodent trapped, on daily basis.

If any rodent is found in the Rodent trap box, concerned supervisor will carefully put rodent in poly bag and will handover to external agency for destroying the rodent outside the factory premises.

If no rodent is trapped in the Trap box; feed of the trap shall be replaced by contractor after every 7 days.

27.0 HEALTH

27.1 Good health of all the employees is one of the most important responsibilities of the organization.

The organization has policy for maintaining the good health of all the employees.

For all employees an annual medical check up shall be conducted by a registered medical practitioner on contract.

This annual medical check up includes any apparent illness, physical examination and test for eyesight, physico-chemical examination of blood and urine, test for any infectious disease.

For all new employees' medical check up shall be carried out at the time of joining the company. If the employee is declared medically fit then only he / she shall be allowed for joining the company.

PHARMA BOOK

SR. NO.	QUESTION ANSWER
28.0	**HYGIENE**
28.1	All employees working either in production or non-production area shall observe a high degree of personal hygiene. All employees shall take bath everyday. All employees shall cut their nails and hair regularly. All employees shall trim their mustache and shave the face regularly. If an employee is with beard, he has to cover the beard with the beard mask. All employees shall wear clean street cloths and street wear everyday. All employees shall wash their hands after using the toilets every time. Any employee having any open lesion on the skin or suffering from any contagious disease shall immediately inform his / her department head. Weekly check of Personnel health and hygiene shall be done and the same shall be recorded in the "Personnel hygiene record" as per Annexure-I. With the consultation of head personnel and administration the employee shall be relieved from the duties till recovery. Chewing of tobacco, pan, gutkha etc. and cigarette / bidi smoking is strictly prohibited within company premises. The security officer shall physically check every employee for the presence of above restricted materials carrying with them. The violation of this shall call for a disciplinary action.

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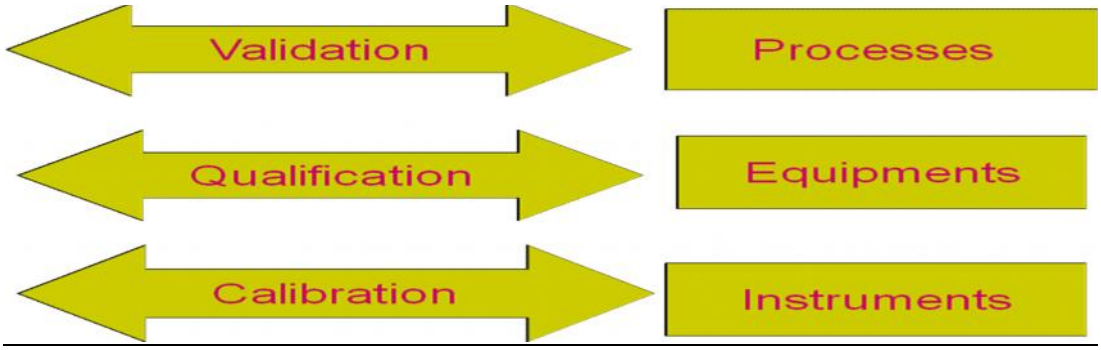
SR. NO.	QUESTION ANSWER
29.0	**QUALIFICATION**
29.1	**What is Qualification** Establishing **documented** evidence which provides a high degree of assurance that a specific process will **consistently** produce a product meeting its **pre-determined** specifications and quality attributes. URS Possibility checked by vendor Purchase order raised by production FDS (Function Design Specification) by Vendor DQ (Design Qualification) by Vendor to Plant Plant / Purchase Approval FAT (Factory Acceptance Test) vendor Visit SAT (Site Acceptance Test) IQ (Installation Qualification) OQ (Operational Qualification) PQ (Performance Qualification) ➢ **USER REQUIREMENT SPECIFICATION (URS)** It is an documented evidence in which user department provide sufficient information to the manufacturer regarding the equipment ➢ **DESIGN QUALIFICATION (DQ)** Documented evidence that the premises, supporting utilities, equipment and processes have been designed in accordance with the requirements of GMP. ➢ **INSTALLATION QUALIFICATION (IQ)** IQ is the documentary evidence to verify that the equipment has been built and installed in compliance with design specifications.

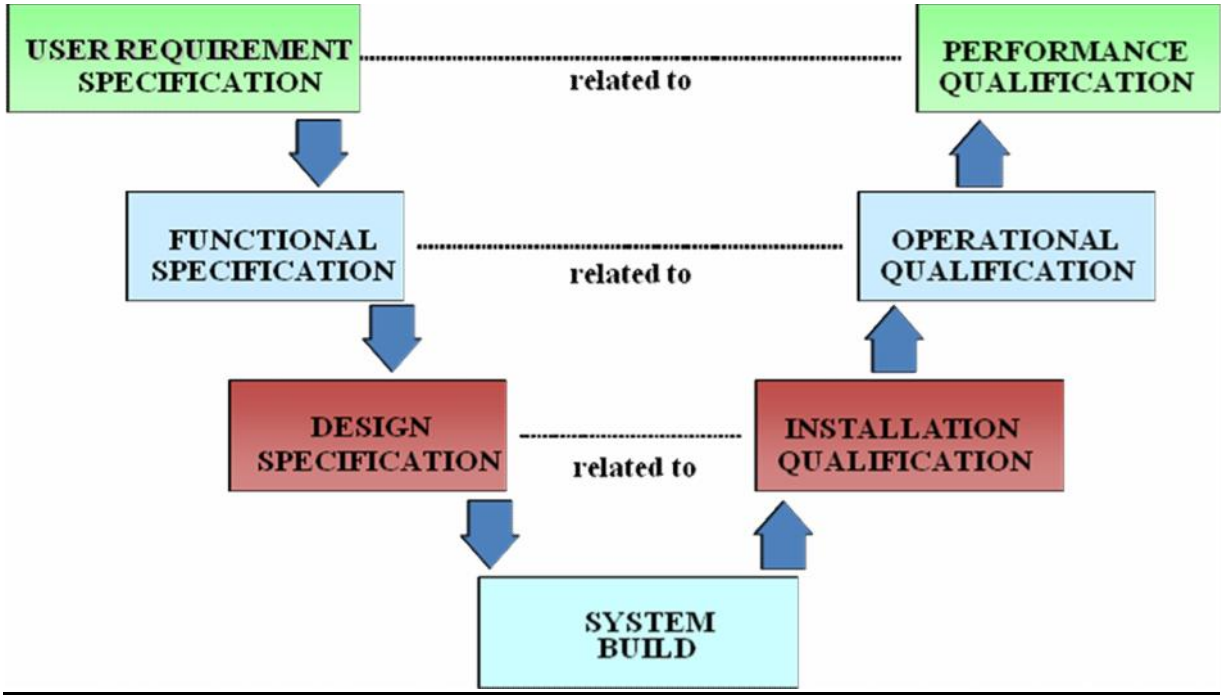
SR. NO.	QUESTION ANSWER

- **OPERATIONAL QUALIFICATION (OQ)**
  OQ is the documentary evidence to verify that the equipment operates in accordance with its design specifications in its normal operating range and performs as intended throughout all anticipated operating ranges.

- **PERFORMANCE QUALIFICATION (PQ)**
  PQ is the documentary evidence which verifies that the equipment or system operates consistently and gives reproducibility within defined specifications and parameters for prolonged periods.

Validation and qualification are essentially components of the same concept. The term qualification is normally used for equipment, utilities and systems, and validation for processes





PHARMA BOOK

SR. NO.	QUESTION ANSWER
30.0	**HVAC SYSTEM**
30.1	**What is HVAC?** Heating Ventilation and Air condition
30.2	**Why Required?** To prevent any cross contamination. For better working environment.
30.3	**Difference between AHU and HVAC?** AHU, which is Air Handling Unit is an appliance used to circulate air HVAC is Heating, Ventilating and Air Conditioning system. HVAC is the central unit to which AHU is connected. AHU is only a part of HVAC HVAC mainly refers to the technology of automotive environmental comfort. The Heating, Ventilating and Air Conditioning system uses the principles of fluid mechanics, thermodynamics and heat transfer. The discoveries of by Michael faraday, Nikolay Lvov, Reuben Trane, William Rankine Wills Carrier, James Joule and Sadi Carnot
30.4	**Type of test for HVAC qualification.** 1. Air Velocity / Air Changes 2. Integrity Test Of HEPA Filters 3. Air borne non-viable particle monitoring 4. Recovery test 5. Smoke test (air flow direction) 6. Measurement of light intensity 7. Measurement of sound level 8. Pressure differential, temperature and relative humidity test 9. Air borne viable particle monitoring by settle plate 10. Air borne viable particle monitoring by air sampler
30.5	**AIR VELOCITY / AIR CHANGES** Instruments: Fan type Anemometer, Hot wire anemometer and Capture Hood.
30.6	**AIR VELOCITY / AIR CHANGES BY CAPTURE HOOD:** **OBJECTIVE** : To verify that the HVAC system is capable of delivering required airflow velocities, airflow volumes and providing required number of air changes. **PROCEDURE :** Take the each filter CFM by capture hood Calculate the number of air changes per hour and record in the raw data format. To calculate the air changes per hour use the following formulas:

SR. NO.	QUESTION ANSWER
	Air Changes per Hour of a Room = $\frac{\text{Total Room CFM X 60}}{\text{Room Volume in Cubic Feet}}$ Attach the reports of air velocities supplied by the party as an attachment **ACCEPTANCE CRITERIA:** Not less than 20 ACPH
30.7	**AIR VELOCITY / AIR CHANGES BY HOT WIRE/FAN TYPE ANEMOMETER:** **Objective:** To verify that the HVAC system is capable of delivering required airflow velocities, airflow volumes and providing required number of air changes. **Procedure:** Ensure that the probe for checking the air velocities is positioned at a distance of not more than 15 cm (6 in.) from the filter face. Measure air velocity from V1 V2 V3 V4 V5 5 locations including four corners and one center. Record the data in a tabulated form and find the average air velocity. **VA = (V1 + V2 + V3 + V4 + V5) / m** Where, **m** : Number of Samples location Taken **VA** : Average air velocity in FPM Air Flow volume in CFM = Average Velocity x Filter Size Calculate the number of air changes per hour and record in the raw data format. To calculate the air changes per hour use the following formulas: Air Changes per Hour of a Room = $\frac{\text{Total Room CFM X 60}}{\text{Room Volume in Cu Ft}}$ **Acceptance Criteria :** Not less than 20 ACPH

SR. NO.	QUESTION ANSWER
30.8	**INTEGRITY TEST OF HEPA FILTERS** **Objective:** To verify the integrity of HEPA filters. **Test Apparatus:** PAO Aerosol generator, Photometer **Procedure:** Introduce the aerosol into the air supplied to the filter. Scan the entire face of each filter including the filter frame using slightly overlapping strokes of the probe, at a traverse rate of NMT 10 feet / minute when using a round probe. Ensure that the probe is held approximately 2.5 cm / 1 inch from the filter face during scanning. Record the observations of PAO leak test in the raw data format. Attach the reports of PAO leak test supplied by the party as attachment. Seal the leakages by using silicon sealant. The extent of filter face observed by silicon sealant should be less then 5% of the filter area, if more is sealed the filter must be rejected and new one shall be installed. Different types of leakages and their corrective actions to be taken are mentioned in the following table. Description of leakage: Leak from the frame and the filter Corrective action to be taken: 1. Tightening the filter frame from all sides 2. If the leak continues to occur, observe the condition of the gasket. If the gasket is damaged, replace the gasket and perform the test again. **Acceptance Criteria:** Leakage should be NMT 0.01%
30.9	**AIR BORNE NON-VIABLE PARTICLE MONITORING:** **Objective** To establish that at different locations within the core process areas, a count of less than specified number of particles per cubic meter of air of 0.5µm or larger is maintained. **Test Apparatus** Air borne particulate counter **Procedure:** The minimum number of sampling point locations is decided as per ISO14644-1, which is detailed as follows: **Derive the minimum number of sampling point locations from the formula: -** $N_L=\sqrt{A}$ Where: $N_{L=}$The minimum number of sampling locations (Rounded up to a whole number) A=The area of the clean room or clean air controlled space in m^2

SR. NO.	QUESTION ANSWER

Where only one sampling location is required, take a minimum of three single sample volumes at that location and calculate and record the average value of the sampled data for each considered particle size.

The single sampling volume in the individual locations is determined by equation

Vs = (20 X 1000) / Cn.m

Where,
Vs : is the minimum single sampling volume (in liters) / location
Cn.m : is the class limit (no of particles / m^3 of air) for the largest considered particle size specified for the relevant class.

Defined no of particles that could be counted if the particle concentration were at the class limit.

Particle count reading at different sampling point locations recorded and the location point to be indicated in room layout drawing.

Record the results of each sampling measurement as the concentration of each of considered particle size appropriate to the relevant classification of air cleanliness.

Determine the overall mean average by the equation
X = (Xl.1 + Xl.2 + Xl.3 + …… + Xl.m) / m
Where,
X : is the overall mean of location averages
M : is the number of individual location averages
Xl.1 to Xl.m : individual location readings

Determine the standard deviation of the location averages by the equation

S = Square Root $(Xl.1 - X)^2 + (Xl.2 - X)^2 + \ldots\ldots + (Xl.m - X)^2 / (m-1)$

Where,
S : is the standard deviation of the location averages.
m : is the number of location taken.

When the number of sampling location is more than 1 and ≤ 9, compute the overall mean of the averages, standard deviation and 95 % Upper Confidence Limit (UCL) from the average particle concentrations for all the location, determine the 95 % upper confidence limit (UCL) for the overall mean using the Equation

$$95\ \%\ UCL = X + \frac{t0.95\ (S)}{\sqrt{m}}$$

t0.95 represent the 95 percentile of the distribution with m–1 degree of freedom

SR. NO.	QUESTION ANSWER

Number of individual averages (**m**)	2	3	4	5	6	7-9
t0.95	6.3	2.9	2.4	2.1	2.0	1.9
When the number of locations is greater than 9, the calculation of a UCL is not required.						

As per ISO 14644-1 If measurements are made at more than one considered particle size, each largest particle diameter shall be at least 1.5 times the next smaller particle diameter. Hence 0.5 µ & 5 µ particle should be considered.

The result of the 95% UCL calculation may fail to meet the specified ISO designation due to the noncompliance caused by a single non random outlier value resulting from an erroneous measurement (due to procedural error or equipment malfunction) or from an unusually low particle concentration (due to exceptionality clean air), the outlier may be excluded from the calculation, provided that:

- The calculation is repeated, including all remaining sampling locations.
- At least three measurement values remain in the calculation;
- No more than one measurement value is excluded from the calculation;
- The suspected cause of the erroneous measurement or low particle concentration is investigated and documented.

Acceptance criteria:

ISO Classification Number	Max. concentration limits (particles / m^3 of air) for particles equal to or larger than the considered sizes	
	0.5µm	**5µm**
ISO 7	**352,000**	**2930**
ISO 8	**35,20,000**	**29,300**

30.10

SMOKE TEST (AIR FLOW DIRECTION):

Objective:
To visualize airflow pattern of process area operation and to prove that there is no cross contamination from one area to the other.

Test Apparatus:
Camera to record the airflow pattern of smoke generator, from third party.

SR. NO.	QUESTION ANSWER
	Procedure: Air flow should be stabilize by running the system for 30 minutes. Generate smoke at the air inlet to the room specified **(**Most critical room has been selected out of the rooms catered by a single AHU). Video shooting or photographs shall be taken to cover the sweeping direction of airflow. Attach the photographs or preserve the CD for reference duly controlled by quality assurance. **Acceptance Criteria:** a. The smoke/fog should be diffused uniformly at supply grill/risers and pass through return terminals. b. There should not be any short-circuiting of airflow, dead pockets and the flow of air should be unidirectional i.e. from supply to return. c. Smoke/fog should pass from area under positive pressure to area under negative pressure
30.11	**RECOVERY TEST (OR DECONTAMINATION TIME):** **Objective:** To determine whether the core process area is capable of returning to its reference specified class within a finite time. **Test Apparatus:** ▪ Calibrated Air borne particle counter ▪ Thermometers and Hygrometers ▪ Magnehelic Gauge **Procedure:** Hold the isokinetic probe of particle counter at the highest particle count location obtained under at rest conditions in each room. Take the particle count and ensure that the particle count is under the specified limit and not the time Continue the particle count and shut down the AHU. Generate the particle count with fogger machine. When particle count goes out of the specified limit (at least 100 times or more than 100 times) note the time. Continue the particle count and start the AHU. Note the time when the particle count of the area reaches to the specified limit. Attach the reports of recovery studies. **Acceptance criteria:** The Recovery time (or decontamination time) shall be not more than 15 minutes.

SR. NO.	QUESTION ANSWER
30.12	**MEASUREMENT OF LIGHT INTENSITY:** **Objective:** To verify the light intensity in different rooms. **Test Apparatus:** Calibrated Lux meter. **Procedure:** Operate the Lux meter as per SOP. Measure the light intensity and record the in test data sheet. **Acceptance Criteria:** Not Less than 500 Lux
30.13	**MEASUREMENT OF SOUND LEVEL:** **Objective:** To verify the sound level in different rooms. **Test Apparatus:** Calibrated Sound Level meter. **Procedure:** Operate the sound level meter as per the SOP. Measure the sound level when there is activity in the areas and record the in test data sheet. **Acceptance Criteria:** Not more than 80 db
30.14	**PRESSURE DIFFERENTIAL, TEMPERATURE AND RELATIVE HUMIDITY TEST:** **Objective:** To demonstrate the capability of the HVAC System to consistently maintain Differential Pressures, Temperatures and Relative Humidity in different rooms. **Test Apparatus:** Magnehelic Gauge, Thermometers and Hygrometers **Procedure:** This test shall be performed after the HVAC System has been operated and the conditions have been stabilized. All the doors in the facility must be closed. Record the Pressure Differential, Temperature and Relative Humidity for a period of 72 hours as per the SOP (Initially at every one hour interval for 8 hrs. and if the observations are within the acceptance criteria continuously for 8 hrs, than record the readings at every four hour interval for remaining 64 hrs.) and record the observation in raw data format.

SR. NO.	QUESTION ANSWER
30.15	**Air Borne Viable Particle Monitoring By Settle Plate :** **Objective:** To determine the viable particle levels in environment of controlled area by settle plate. **Test Instrument/Sampling aids:** Media plates **Procedure:** Test shall be performed at operation condition by the microbiologist. Prepare the SCDA and SCA plate and enter in to the respective area as per Entry and Exit procedure. Expose the plates at various locations as per the settle plate location layout. The plate exposure shall be carried out for the controlled area for three consecutive days after taking the particle count. After completion of plate exposure, SCDA Plate incubate at 30-35°C for 48 hours and SCA plate incubate at 20-25°C for 5 days. After incubation observe the results and record in the data sheet. **Acceptance Criteria**

Plates	Alert Limit	Action Limit
Total Bacterial Count	NMT 60 cfu / plate	NMT 100 cfu / plate
Total Fungal Count	< 1 cfu / plate	< 1 cfu / plate

<table>
<tr><th>SR. NO.</th><th>QUESTION
ANSWER</th></tr>
<tr><td>30.16</td><td>
Air Borne Viable Particle Monitoring By Air Sampler :

Objective:
To determine the viable particle levels in environment of controlled area by Air Sampler.

Test Instrument/Sampling aids:
Air Sampler (Hi Media)

Procedure:
Test shall be performed at operation condition by the microbiologist.

Prepare the SCDA plate and enter in to the respective area as per Entry and Exit procedure.

Place the SCDA plate on air sampler and operate the air sampler as per SOP No. QCG 179.

Take sampling volume 1000 liter of air as per sampling plan.

After completion of sampling incubate the SCDA plate at 20-25ºC for 72 hours and further transfer at 30-35ºC for 48 hours.

After incubation observe the results and record in the test data sheet.

Acceptance Criteria
<table>
<tr><td>Class A</td><td>< 1 cfu / M^3</td></tr>
<tr><td>Class B</td><td><10 cfu / M^3</td></tr>
<tr><td>Class C</td><td><100 cfu / M^3</td></tr>
<tr><td>Class D</td><td><200 cfu / M^3</td></tr>
</table>
</td></tr>
<tr><td>30.17</td><td>Difference between Settle Plate and Air sampling

Settle Plate – Passive Particle

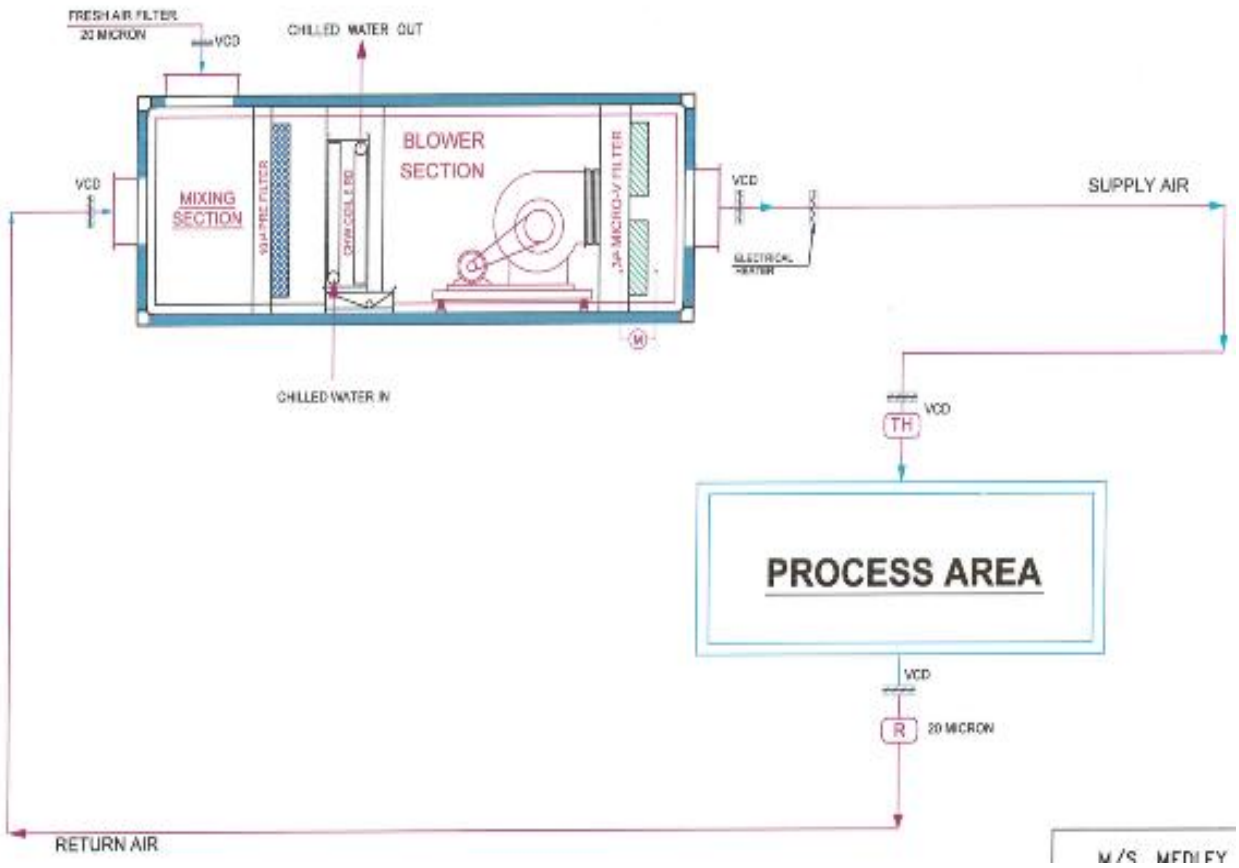
Air Sampling – Active sampling</td></tr>
<tr><td>30.18</td><td>Which Guideline follows

ISO 146441</td></tr>
<tr><td>30.19</td><td>Re-Qualification Frequency

1 year ± 30 Days</td></tr>
<tr><td>30.20</td><td>If out of limit

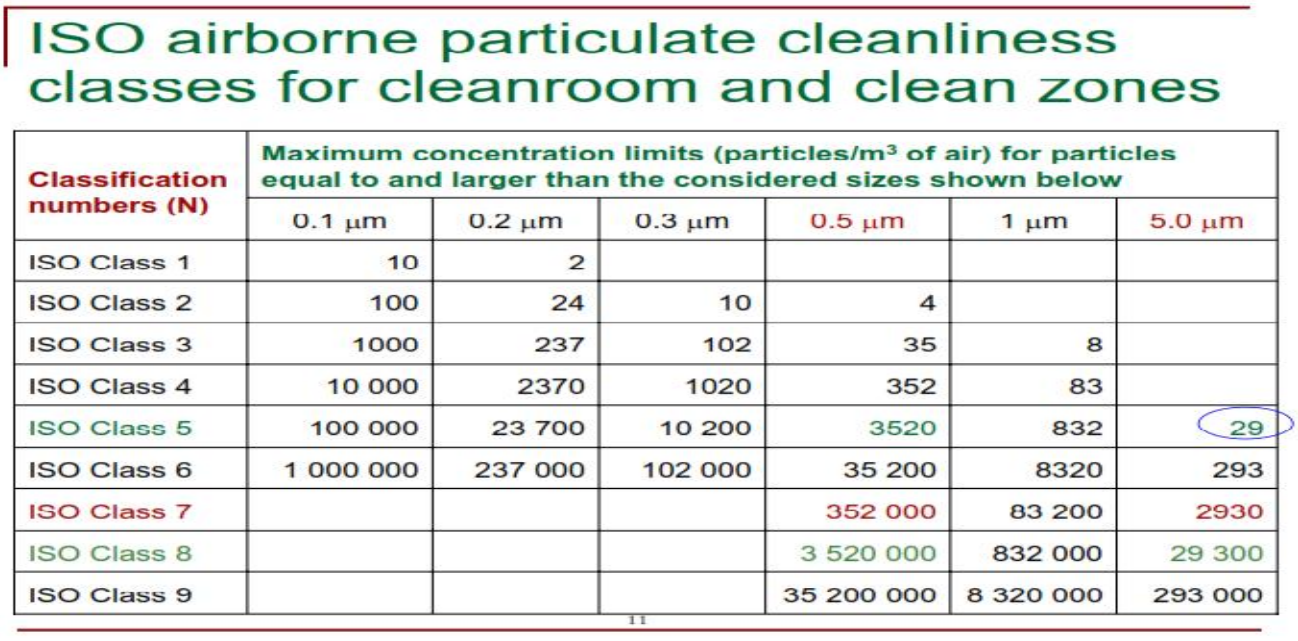
Deviation to be raised, Deviation trough failure investigation, investigation trigger CAPA, through CAPA change control to be raised (if required).</td></tr>
</table>

PHARMA BOOK

SR. NO.	QUESTION ANSWER
30.21	**GENERAL FLOW** 
30.22	

<table>
<tr><th>SR. NO.</th><th>QUESTION
ANSWER</th></tr>
<tr><td>30.23</td><td>Filtration Rating

Each AHU with 10 micron fresh air filter, 10 micron pre filters, 3 micron intermediate filters, Terminal HEPA 0.3 micron filters efficiency of 99.997% in core areas and HEPA filter in return. Exhaust HEPA Filter.</td></tr>
<tr><td>30.24</td><td>Air Circulation

90% and 10% fresh air.</td></tr>
<tr><td>30.25</td><td>Difference between ISO and EU particle count
As per federal Particle count
<table>
<tr><th colspan="3">At Rest</th><th colspan="2">In Operation</th></tr>
<tr><td>Class</td><td>0.5 µm</td><td>5.0 µm</td><td>0.5 µm</td><td>5.0 µm</td></tr>
<tr><td>100</td><td>100</td><td>0</td><td>100</td><td>0</td></tr>
<tr><td>1,000</td><td>1,000</td><td>7</td><td>10,000</td><td>70</td></tr>
<tr><td>10,000</td><td>10,000</td><td>70</td><td>1,00,000</td><td>700</td></tr>
<tr><td>1,00,000</td><td>1,00,000</td><td>700</td><td>Not Defined</td><td>Not Defined</td></tr>
</table>
As per ISO Particle count
<table>
<tr><th colspan="3">At Rest</th><th colspan="2">In Operation</th></tr>
<tr><td>Class</td><td>0.5 µm</td><td>5.0 µm</td><td>0.5 µm</td><td>5.0 µm</td></tr>
<tr><td>ISO CLASS 5</td><td>3520</td><td>29</td><td>3520</td><td>29</td></tr>
<tr><td>ISO CLASS 6</td><td>35,200</td><td>293</td><td>3,52,000</td><td>2930</td></tr>
<tr><td>ISO CLASS 7</td><td>3,52,000</td><td>2930</td><td>35,20,000</td><td>29,300</td></tr>
<tr><td>ISO CLASS 8</td><td>35,20,000</td><td>29,300</td><td>Not Defined</td><td>Not defined</td></tr>
</table>

ISO airborne particulate cleanliness classes for cleanroom and clean zones
<table>
<tr><th rowspan="2">Classification numbers (N)</th><th colspan="6">Maximum concentration limits (particles/m³ of air) for particles equal to and larger than the considered sizes shown below</th></tr>
<tr><th>0.1 µm</th><th>0.2 µm</th><th>0.3 µm</th><th>0.5 µm</th><th>1 µm</th><th>5.0 µm</th></tr>
<tr><td>ISO Class 1</td><td>10</td><td>2</td><td></td><td></td><td></td><td></td></tr>
<tr><td>ISO Class 2</td><td>100</td><td>24</td><td>10</td><td>4</td><td></td><td></td></tr>
<tr><td>ISO Class 3</td><td>1000</td><td>237</td><td>102</td><td>35</td><td>8</td><td></td></tr>
<tr><td>ISO Class 4</td><td>10 000</td><td>2370</td><td>1020</td><td>352</td><td>83</td><td></td></tr>
<tr><td>ISO Class 5</td><td>100 000</td><td>23 700</td><td>10 200</td><td>3520</td><td>832</td><td>29</td></tr>
<tr><td>ISO Class 6</td><td>1 000 000</td><td>237 000</td><td>102 000</td><td>35 200</td><td>8320</td><td>293</td></tr>
<tr><td>ISO Class 7</td><td></td><td></td><td></td><td>352 000</td><td>83 200</td><td>2930</td></tr>
<tr><td>ISO Class 8</td><td></td><td></td><td></td><td>3 520 000</td><td>832 000</td><td>29 300</td></tr>
<tr><td>ISO Class 9</td><td></td><td></td><td></td><td>35 200 000</td><td>8 320 000</td><td>293 000</td></tr>
</table>
11</td></tr>
</table>

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<table>
<tr><th>SR. NO.</th><th>QUESTION
ANSWER</th></tr>
<tr><td>30.26</td><td>Action in case of power failure

10 minutes</td></tr>
<tr><td>30.27</td><td>Total AHU

Total 41 – AHU</td></tr>
<tr><td>30.28</td><td>Cooling system

Condensing unit and chiller system</td></tr>
<tr><td>30.29</td><td>HVAC Limit

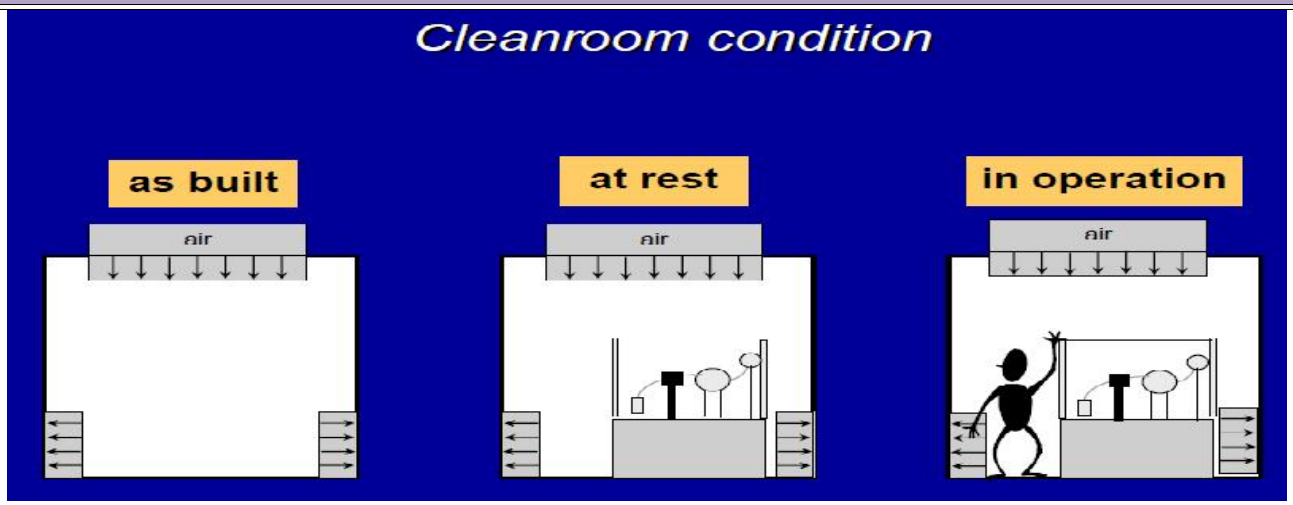
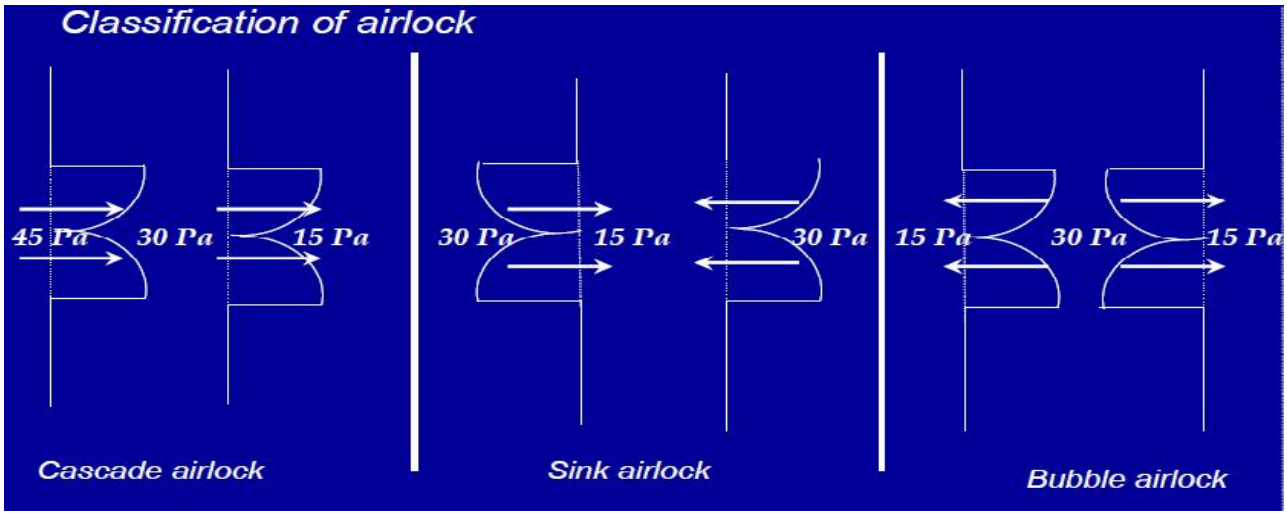
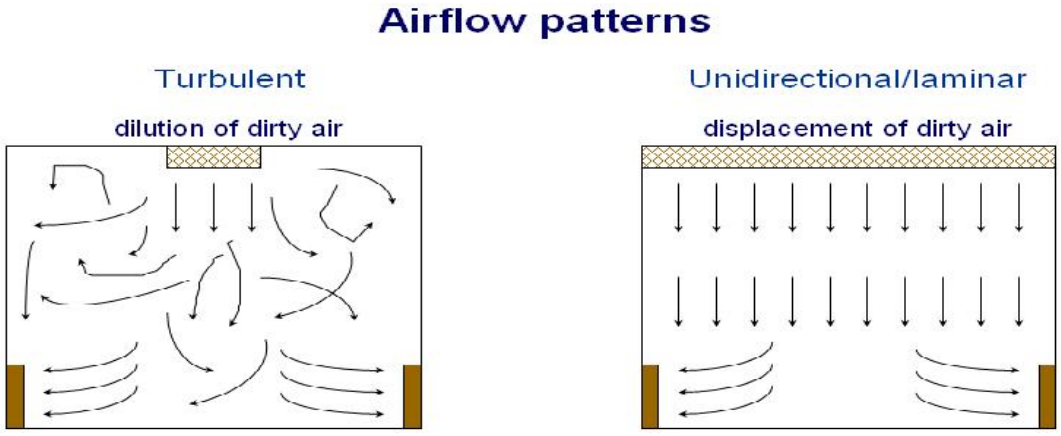
ACPH NLT 20.
HEPA filter Integrity NMT 0.01%
Sound level should not be more than 80 db.
Light intensity should not be less than 500 lux.

Particle count
<table>
<tr><th colspan="3">At Rest</th><th colspan="2">In Operation</th></tr>
<tr><td>Class</td><td>0.5 µm</td><td>5.0 µm</td><td>0.5 µm</td><td>5.0 µm</td></tr>
<tr><td>ISO CLASS 7</td><td>3,52,000</td><td>2930</td><td>35,20,000</td><td>29,300</td></tr>
<tr><td>ISO CLASS 8</td><td>35,20,000</td><td>29,300</td><td>Not Defined</td><td>Not defined</td></tr>
</table>
25± 2°C for processing and secondary packing area
NMT 25°C for Quarantine and Empty Capsule store area
55 ± 5% for processing area. NMT 60% for Quarantine and 35% to 60% for Empty Capsule store area

Viable particle count
LIMITS ALERT ACTION
BACTERIAL 60 CFU/Plate 100 CFU/Plate
FUNGAL < 1 cfu / plate < 1 cfu / plate</td></tr>
<tr><td>30.30</td><td>Filter Cleaning

Clean with 1.5 kg/cm2 filtered air and wash with potable water and dry with potable water
Frequency : Pre filter – Weekly
Micro V Filter – Monthly
Return Filter – At the time of time B cleaning by production or when area is idle for 10 days
Equipment Filter – Monthly</td></tr>
<tr><td>30.31</td><td>Differential Pressure across filter
Differential Pressure across 10µ filter should be in range 2 to 12 mm of wc
Differential Pressure across 3µ filter should be in range 2 to 15 mm of wc</td></tr>
<tr><td>30.32</td><td>HEPA filter replacement frequency

24 month ± 1 month</td></tr>
</table>

SR. NO.	QUESTION ANSWER
30.33	  

PHARMA BOOK

SR. NO.	QUESTION ANSWER
31.0	**RLAF/LAF**
31.1	**What is RLAF / LAF** **RLAF -** Reverse Laminar Air Flow **LAF -** Laminar Air Flow
31.2	**Difference between RLAF/LAF**
31.3	**Which Guideline** ISO 146441
31.4	**Air Circulation**
31.5	**Filtration Rating** Each RLAF was found affixed with 10 micron pre filters, 3 micron intermediate filters, final HEPA filters and 20 Micron return filters.
31.6	**Qualification Frequency** 6 Month ± 30 Days
31.7	**Test** 1. Air velocity, 2.Integrity of HEPA filters, 3.Particle count at rest, 4. Sound Level test, 5. Light intensity test, 6. Viable Particle Monitoring. 7. Recovery Test 8. Smoke Test (Air Flow Direction)
31.8	**RLAF/ LAF Manometer Pressure Reading** 7-15 mm of water column

SR. NO.	QUESTION ANSWER

Test Limit :

Air Velocity 90 ± 20 FPM
HEPA filter Integrity NMT 0.01%
Sound level should not be more than 80 db.
Light intensity should not be less than 500 lux.

Particle count

At Rest			In Operation	
Class	0.5 µm	5.0 µm	0.5 µm	5.0 µm
ISO CLASS 5	3520	29	3520	29

By Settle Plates / Contact Plates		
Plates	**Alert Limit**	**Action Limit**
Total Bacterial Count	< 1 cfu / plate	< 1 cfu / plate
Total Fungal Count	< 1 cfu / plate	< 1 cfu / plate

By Air Sampler	
Class A	< 1 cfu / M^3

31.9

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PHARMA BOOK

SR. NO.	QUESTION ANSWER
32.0	**WATER SYSTEM**
32.1	**Make :** Thermax Ltd. **Source of Water -** Bore well **Depth of bore well** – 150 ft. **Capacity :** EDI 3.5 M^3 / Hr , Under Ground Storage Tank : 27 M^3, Purified Water storage Tank : 7 KL
32.2	**Return line temperature** SANITIZATION –AOBVE 85, GENERAL – AMBIENT (25 -30)
32.3	**Sanitization frequency** EDI and Distribution – Weekly RO – 15 Days
32.4	**Preventive maintenance** MONTHLY
32.5	**Revalidation criteria:** 3 Years ± 1 Month or any significant change in • Water treatment system -Design • Location • Capacity • Regulatory requirement
32.6	**If any instruments Failure then?**
32.7	**Out of limit what will happen**
32.8	**Use of Equipment** Hypochlorite dosing Garnet Filter Sodium Metabisulfite Dosing Anti Scalant Dosing (For Scale Prevention) Acid Dosing

SR. NO.	QUESTION ANSWER
	pH Dosing FILTER RO EDI UV Conductivity Temperature Indicator **HYPOCHLORITE DOSING SYSTEM** Hypochlorite solution dosing can be done on line in the raw water with help of dosing pump for disinfection. 10% Solution of Hypochlorite is available of which is dissolved in permeate water. **MULTI GRADE SAND FILTER (MGSF)** Filtration of water for removal of suspended impurities **SODIUM METABISULFITE DOSING:** Sodium Metabisulfite Dosing is dosed in this water to dechlorinate the water. **SOFTENER :** Softener to remove the heavy metals & minerals. **ANTI SCALANT DOSING (FOR SCALE PREVENTION)** An Antiscalant Chemical Permacare - 191 dosed on line in the Filtered Water by Dosing Pump to prevent the formation of Scale on the surface of Membrane elements It extend the solubility of sparingly salts like : $CaSO_4$, $CaCO_3$ & $BaSO_4$ etc. **FILTER** Micron Cartridge filtration system is provided in the pretreatment section as a polishing filtration step for removal of fine particulate **VENTFILTER.** Sanitary vent filter with a 0.2 –micron cartridge has been provided at the top of the tank to breath bacteria free air. MOC of cartridge filter will be PTFE, Hydrophobic.

SR. NO.	QUESTION ANSWER
	CHEMICAL– CAUSTIC SODA DOSING (FOR PH ADJUSTMENT) To adjust pH of raw water upto 7.5 caustic soda (NaOH) dosing is done on line by means of Metering Type dosing pump with inbuilt pH meter. Caustic soda (NaOH) solution is prepared by taking 45 liters permeate water in the solution preparation tank & dissolving 22 gm. caustic soda (100 % Flakes) for 24 Hrs operation. The solution on line at the flow rate of 2.0 Liters per hour or as required in the clean & clear Raw Water flowing at the rate of 1.0 M3/Hr. **CEDI (CONTINUOUS ELECTRO- DEIONIZATION):** CEDI system is well established water purification technology by electro-dialysis & ion-exchange resin. Deionization Consistently produces purified water of very low conductivity. Conductivity of water of outlet of CEDI module is between 0.1 to 1.0 micron siemens/cm. **UV STERILIZER** This has been provided to control microbial growth in the water. This unit will operate at the flow rate of 2800 LPH and it will emit the UV rays of 254 nm. It will give out put of three-log reduction. UV will be switched off during sanitization. **SANITIZATION SYSTEM:** If the microbial load is higher than the alert limit, the loop system needs to be sanitized. For sanitization purpose, a steam heat exchanger is provided. The storage and distribution system is sanitized at 85°-90° C for one hour (to be established). The frequency of hot water sanitization is once in a week (to be established) or whenever the microbial counts exceed the alert limit. **PRESSURE TEST** Hydro test followed by flushing of piping system with chlorine free water (preferably DM water) to remove dirt and other foreign particles. Pressure test will be done 1.5 times the operating pressure Pressure drop is observed during the test for the duration & based on pressure drop it is concluded acceptable or not acceptable **CLEANING AND PASSIVATION** Cleaning medium is compatible with 0.5micron surface finish. Cleaning is mandatory. Passivation is mandatory. Use of 1% volume/volume Nitric acid solution in water and is circulated for 8-10 hours and operated according to a written pre-approved procedure. On line pickling/passivation is carried out as per written pre-approved procedure and the same is documented. **RINSING** The system will be filled with the purified water and circulated at 15 minutes and will be flushed at each user point outlet and equipment connection thoroughly. Then again the system is rinsed with purified water until the pH is balanced with inlet pH and conductivity the range of supply conductivity.

SR. NO.	QUESTION ANSWER
	WELD JOINTS All the weld joints will be butt-welded by Manual TIG welding without external filler wire (butt welded). For purging, Argon gas with a purity of min. 99.9998% will be used. Ferrous material, tools or equipment (carbon steel cutting tools) in the fabrication or installation of system will not be used. **TOC ANALYZER** The Thornton 5000TOC Total Carbon Sensor and 770MAX meter measures the amount of organic carbon in high purity waters by organic carbon to CO2 with appropriate UV radiation. The resulting increase between two temperature compensated conductivity measurements of the sample flow stream at points before and after oxidation is used to calculate the amount of organic carbon present. Throughout the test procedure, the units " ppb " or carbon and micrograms Carbon/L will appear.
32.9	**Test** Instrument Verification Piping Verification Welding Surface Finish Deadleg Measurement Slope Measurement Hydro Test Passivation Sanitization
32.10	**WELDING** **OBJECTIVE** To establish a Standard Operating Procedure for Orbital Welding. **SCOPE** This shall be applicable to the Piping of PFW Storage & Distribution System. **RESPONSIBILITY** To do : Manufacturer. To Check : User company **ACCEPTANCE CRITERIA** All joints shall be argon welded wherever possible. The welder is qualified / certified. Weld Numbers and TC joints to be indicated on the as-built Isometric. **WELDING (Standard Operating Procedure)**

SR. NO.	QUESTION ANSWER
	ALIGNMENT OF TUBING To do welding secure tubing in pipe stand or tripod etc. using two stands per tube. Use SS Shims and do not allow direct contact of tubing with carbon steel material. **Following rules should be followed during alignment:** Make alignment so that welding will be done in horizontal position. Accurately level the tubing using care and precision level of at least 18" in length and ensure that the matching faces are in contact with no perceptible gap. **TACKING** To hold pieces together for final orbital welding, pre-tacking will be done. Tacking should be small to allow them to be completely integrated into the final weld. Observe penetration and crack at tacking. Clean OD only with fine k-2 pest / scotch bright just prior to the final weld. **WELDING** Clamp the welding head at position of welding joint. Centre the tungsten tip over the weld joint contact surface. Attach the purge gas source to the open end of the system being welded. Probably that point is the lowest point & purge gas vent point at the opposite end to the gas source point. Check the Argon gas (99.99%) flow rate to head and to purging. Check the programming which includes the speed, current, overlapping, turn, pulse, pre gas purging time, post gas purging time & the strike current and compare that selected program to the pipe sample joint. **CHECK POINTS** Weld should be fully penetrated around the entire weld parameter with no crevices or entrapment sites. Weld shall be smooth uniform, complete and flat, not concave on the outside. Weld shall have a uniform and complete weld bead width on the inside with no Convexity. There shall be no visible signs of oxidation discoloration of the inner weld There shall be no porosity, pinhole and cracking. Re welding of defective weld shall not be carried out in case of above defects.

SR. NO.	QUESTION ANSWER

SURFACE FINISH MEASUREMENT Ra

OBJECTIVE:
To establish a Standard Operating Procedure for Ra Value Measurement.

SCOPE:
This shall be applicable to Ra Value Measurement of the PFW Storage & Distribution system.

RESPONSIBILITY:
To do : Manufacturer.
To Check : User company

ACCEPTANCE CRITERIA:
Internal surface of piping, fittings, tank, etc. shall be electro polished and Ra Value shall be less than or equal to 0.8 micrometer.

External surface of piping, fittings, tank, etc. shall be less than or equal to 1.2 micrometer.

PROCEDURE:
General Check.
Check the Power Supply.
Connect the display unit to single phase power supply through AC adaptor. (Input AC 240V, 50 Hz, 9W Output DC 9V, 500mA)
Then connect drive /detector unit to display unit with the help of a connecting cable.

Press the **ON/OFF DATA SWITCH** on the Display Unit, which will switch ON the screen where we can check the following parameters to measure the Ra Value:-

- Check parameter is **Ra**.
- Unit of parameter is «**m**.
- Cut-off length is **0.8**.

Insert the detector. Attach the support feet as per the surface to be measured.
Set the detector parallel to the surface to be measured.
Set the direction of the lay, if any, square to the measuring direction.
Be sure to set the skid in contact with the surface to be measured.
Press the START/STOP button and the measurement is initiated after error checking, string goes out, segment by segment indicating detector travel during measurement.
Once the travel is completed for the specified traversing length, the measured value is displayed on the screen and the detector returns to the initial point and stops.

1. If there is any error message, message ‘E’ during measurement, then check the following things and the after rectification starts again.
2. Poor connection of the connector.
3. Faulty detector installation.
4. Measure the reading when the Input data exceeds the measurable range.
5. Measure the reading surface at any given point and get the value as the final Ra Value.

Note: Sampling plan will be as per √n+1 logics heat number wise.

SR. NO.	QUESTION ANSWER
	DEAD LEG MEASUREMENT*:*

OBJECTIVE:
To establish a Standard Operating Procedure for dead leg measurement.

SCOPE:
This shall be applicable to dead leg measurement for PFW Storage & Distribution System

RESPONSIBILITY:
To do : Manufacturer.
To Check : User company

PROCEDURE:
Dead leg measurement (main pipe and branch having equal diameter)

Measure the distance from inner surface of main pipe to the farthest end of the branch (till the dead end, in case of valve consider till center point of valve body)

Dead leg measurement (main pipe and branch having unequal diameter)Measure the distance from inner surface of main pipe to the farthest end of the branch (till the dead end, in case of valve consider till center point of valve body)

NOTE: RECORD THE ABOVE RESULTS OBTAINED

ACCEPTANCE CRITERION:
The dead leg shall be less than or equal to 3d (d stands for diameter of branch tapping)

SR. NO.	QUESTION ANSWER

SLOPE MEASUREMENT

OBJECTIVE:
To establish a Standard Operating Procedure for Slope measurement.

SCOPE:
This shall be applicable to Slope Measurement of PFW Storage & Distribution System.

RESPONSIBILITY:
To do : Manufacturer.
To Check : User company

PROCEDURE:

GENERAL:
Make a continuous water column in a transparent and flexible U-tube.

Keep one end of the U-tube at the starting point of the subjected tubing/line, such that the water meniscus should be leveled with the axis of the subjected tubing/line.

Keep other end of the U-tube at the end point of the subjected tubing/line.

Measure the distance between the starting point & the end point of the subjected tubing/line(**X**).

Measure the distance between the tubing /line axis & the water meniscus at the end point(**Y**).

Now calculate the ratio of **Y: X**. the ratio should be more than **1:100**.

If the ratio is less than the desired value, then the level of the subjected section should be adjusted accordingly.

ACCEPTANCE CRITERIA:

Slope of the line : Slope should not be more than 1:100 in any section of line.

SR. NO.	QUESTION ANSWER

HYDROTEST

OBJECTIVE:
To establish a Standard Operating Procedure for Hydro test.

SCOPE:
This shall be applicable to Hydro test of the PFW Distribution Line.

RESPONSIBILITY:
To do : Manufacturer.
To Check : User company

PROCEDURE:

GENERAL
Fill Purified water in the tank up to 40% of the total Tank Volume of the storage. Close all the drain points & the POUs in the system.

Select the system in manual mode.

Select the Pump & start it in manual mode.

Slowly close the return line of the diaphragm valve and then close the pump discharge valve. Meanwhile stop the pump and see that there is pressure rise in the line.

Pressurize the entire loop with the help of Hydro pump (1.5 times the operating Pressure).

Set the pressure as per requirement.

Wait for 1 hour and check the pressure. If there is no drop in pressure, the loop Hydro test is successful. If there is pressure drop then rectify it and repeat the Hydro test as per the above point.

ACCEPTANCE CRITERIA

There should not be any leakage. & There should not be any pressure drop during hold time.

SR. NO.	QUESTION ANSWER

PASSIVATION

OBJECTIVE:
To establish a Standard Operating Procedure for Passivation.

SCOPE:
This shall be applicable to Passivation of tubes, for PFW Storage & Distribution System.

RESPONSIBILITY:
To do : Manufacturer.
To Check : User company

PROCEDURE:

GENERAL
This specification covers requirement for cleaning, and to passivate of all stainless steel or alloys containing more than 12% Cr.

All the welding flux and weld spatter shall be removed by initial cleaning.

INITIAL CLEANING
Take 25-50% volume of water in the Storage Tank (of the water quality –chlorine content less than 5ppm). Re-circulate the water for a period of 30 minutes.

Drain the water in the Storage Tank by opening the drain valve and in the System by opening the lowest point valves.

PASSIVATION
The composition of the passivating Bath shall be as follows:-

1. 1 % concentrated Nitric acid,
2. 99% Purified Water
3. 1.5 times the hold up volume of the distribution piping, and
4. 1.5 times the hold up volume of the equipment in the loop (except tanks) **OR** 25% volume of the Storage Tank whichever is **Higher**

Tank pipes and other equipments shall be filled with the solution. The solution shall be held in the equipment or re-circulated. **Atmospheric 8-10 hours**

Stop the recirculation.

Drain the acid solution in the Storage Tank by opening the drain valve and in the System by opening the lowest point valves.

Flush the system with fresh Purified water till the whole acid solution is flushed out.

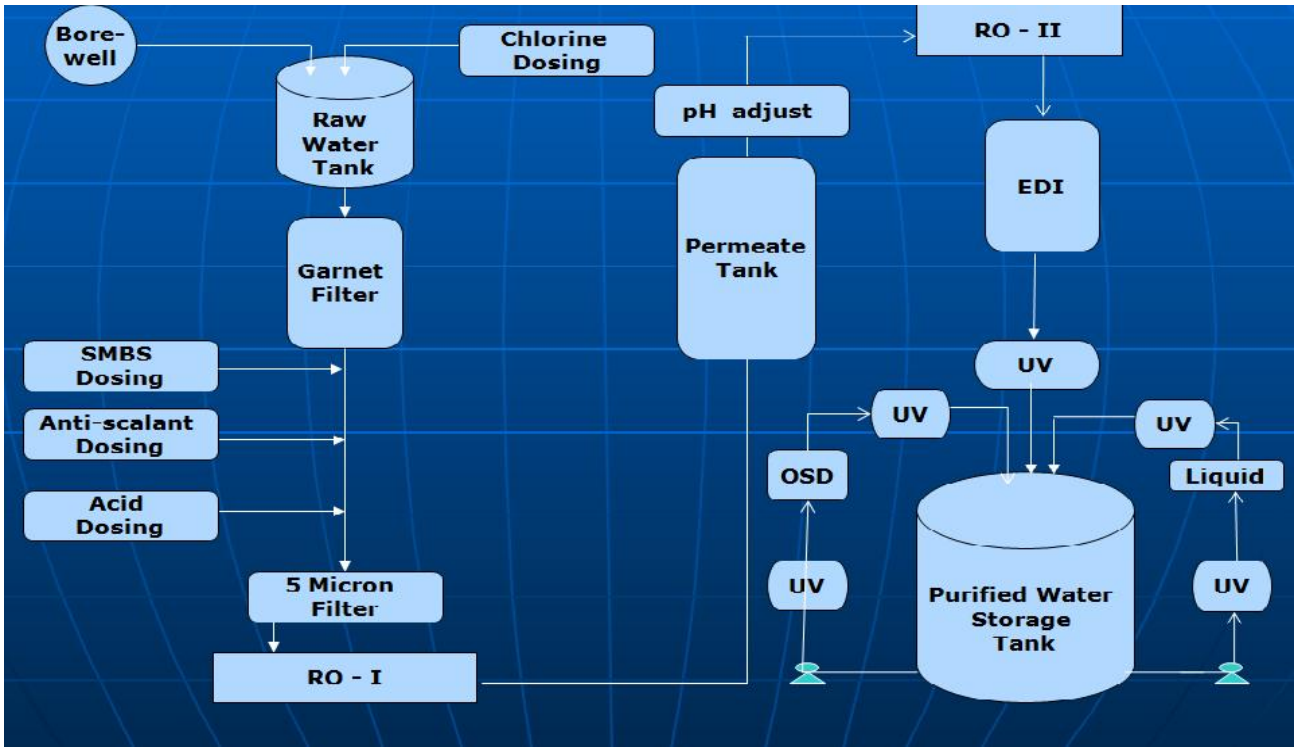
SR. NO.	QUESTION ANSWER
	FINAL CLEANING Take 25-50% volume of water in the Storage Tank (of water quality– chlorine content less than 1ppm). Re-circulate the water for a period of 30 minutes. Drain the water in the Storage Tank by opening the drain valve and in the System by opening the lowest point valves. Repeat the above procedure (4.4.1 & 4.4.2) till the Conductivity gets to <3.o μs/cm^2 This will end the cleaning cycle. **WATER QUALITY TEST DURING FLUSHING** Check the Conductivity and HNO3 Concentration of supply line of water and return line of water. pH of the water should be between 5 to 7 and feed and drain water pH should match. **ACCEPTANCE CRITERIA**: After line-flushing pH at loop return shall match with in feed water quality.

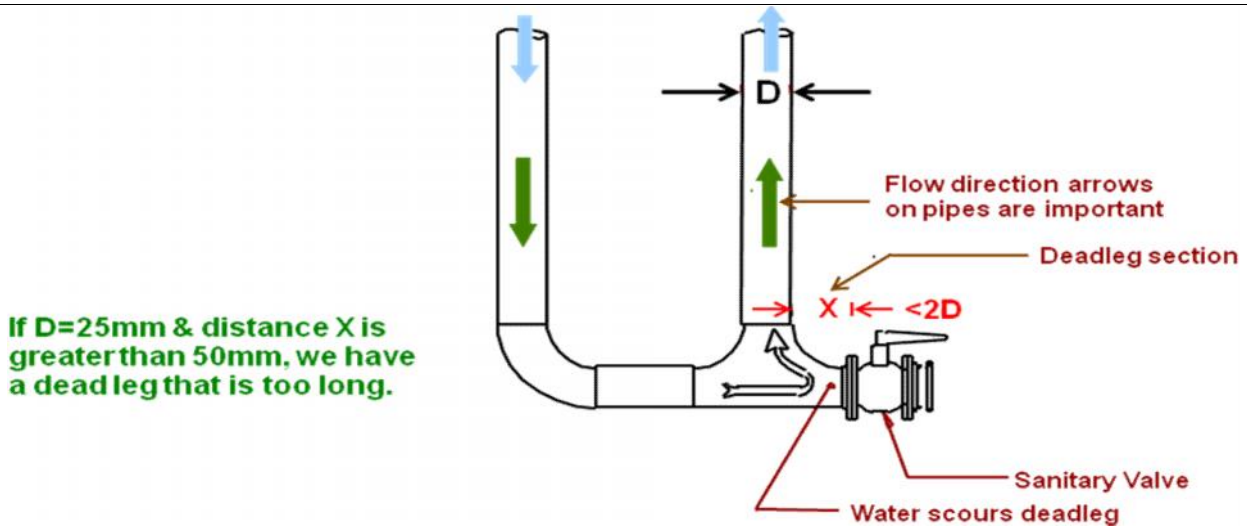
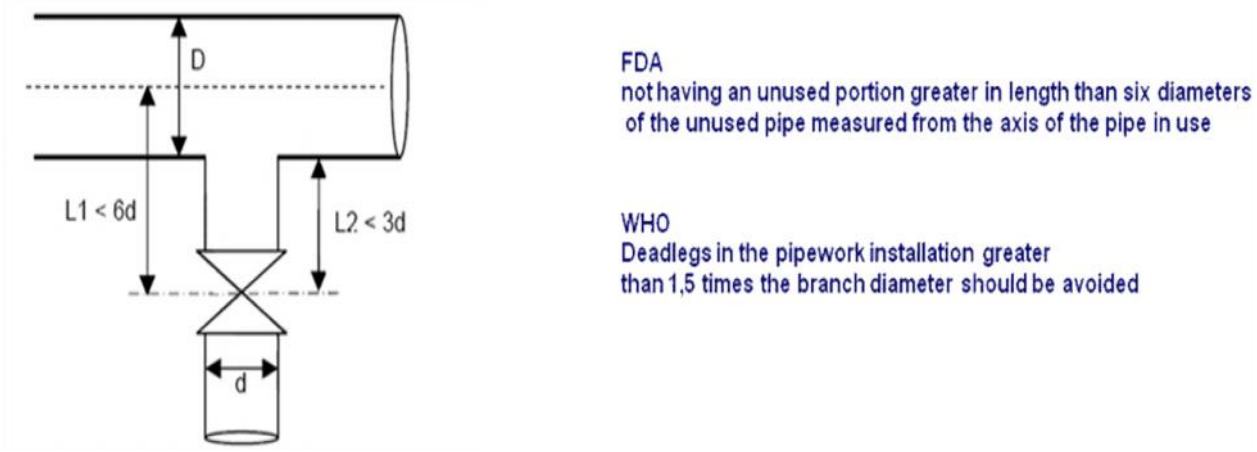
SR. NO.	QUESTION ANSWER
	SANITIZATION **OBJECTIVE:** To sanitization the loop and Storage Tank. **SCOPE:** This shall be applicable to the sanitization of PFW Distribution Piping and Storage Tank. **ACCEPTANCE CRITERIA:** PFW water Temperature shall not be less than 80 °c PFW water Circulation time should be no less than 30 minutes. **PROCEDURE:** Purified water storage & distribution system has been designed for Hot Water sanitization @ 85ºC.The frequency of the sanitization shall be determined during Phase-I and Phase-II trials but would normally be once every week. (Description Will Be provided in OQ) **ACCEPTANCE CRITERIA:** **Sanitization of loop :** Hot water sanitization should be done by recirculation PFW water in system. First raised PFW temp to 80 ° and maintain it above 80 ° with help of Plant steam heating at tank jacket. Recirculation time should not be less than 30 minutes.
32.11	**Dead leg (As per Guideline)** USFDA MHRA Schedule M WHO
32.12	**IP/BP/USP Purified Water Specification** pH – (5-7 at 25ºC), Micro (NMT100cfu/ml)
32.13	**Specification Criteria (Feed Water, Purified Water)** Feed Water pH – 6.5 to 8.5 TDS – 2000 ppm Hardness – 600 ppm Chloride – 1000 ppm Conductivity – Purified Water

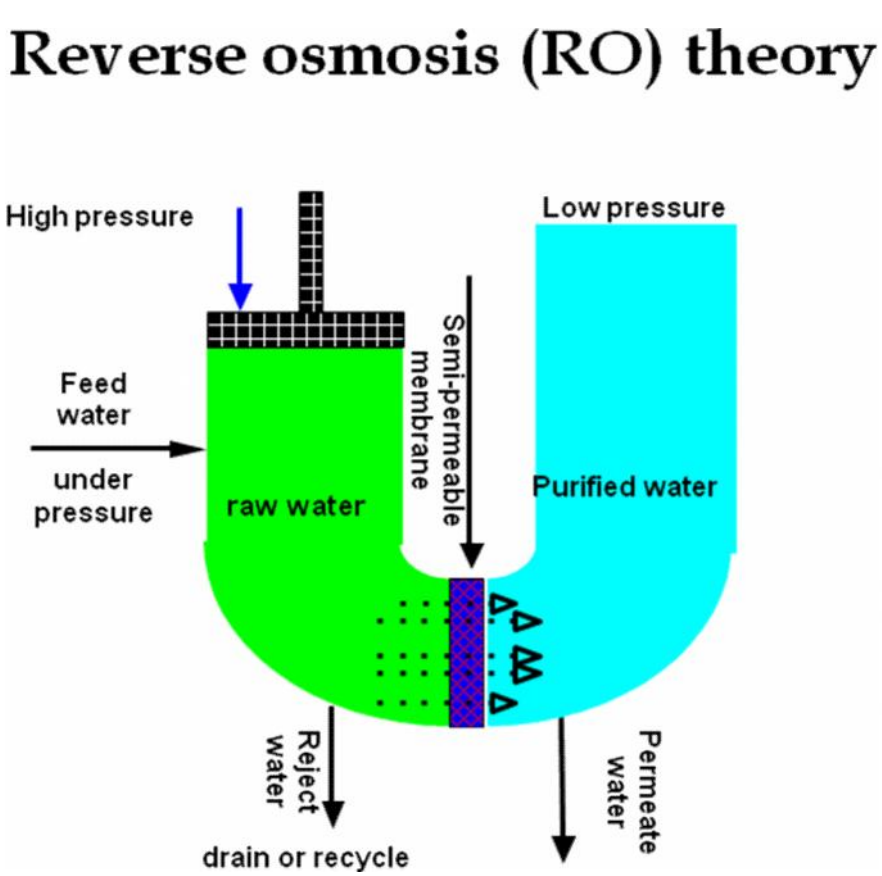
PHARMA BOOK

SR. NO.	QUESTION ANSWER
32.14	**TYPES OF WATER** **Following types of water are used in the factory premises** ➢ **Raw Water:** Raw water may be used in the early stages of cleaning of pharmaceutical manufacturing equipments. It is the prescribed source feed water for the production of purified waters. **Chemical formula: H_2O** ➢ **Drinking Water** Raw water (potable water) is used for drinking purpose and stored in water Cooler through Aqua Guard Water Purification system. ➢ **Purified Water** Purified water is used as an excipient in pharmaceutical formulations beside its application in cleaning of equipment,area etc.
32.15	**Total Sampling/User Point** Sampling Point – 36 User Point – 21 (Tablet - 9, Liquid -9, QC – 3)
32.16	**Sanitization** Once in a week at not les than 85° C.
32.17	**The microbial limit** NMT 100 CFU/ml
32.18	**Phase wise Validation** Phase I – Every sampling point on daily basis for one month Phase II - Every sampling point on weekly basis for 3 month Phase III - Every sampling point on fortnightly basis for 1 year
32.19	**Loop System** Zero dead leg
32.20	**Tank Cleaning frequency** Once in month

PHARMA BOOK

SR. NO.	QUESTION ANSWER
32.21	**FLOW OF WATER SYSTEM** 
32.22	**Preparation of chemicals** **Sodium Hypo chloride (NaOCl)** 80 liters water +1.2 kg Sodium Hypochlorite Adjust the strokes 55% (i.e. 3.3 LPH) to get the 0.5 to 1-PPM free residual chlorine **Sodium meta bi sulphite (SMBS)** 80 liters water +360 grams Sodium Meta Sulphite 55% (i.e 3.3 LPH) to achieve ORP meter reading less than 500 mV. **Hydrochloric Acid (HCl)** 80 liters water + 47.6 grams Hydrochloric Acid dosing rate 55% (i.e 3.3 LPH) to achieve RO inlet pH 5.0 to 6.0. **Antiscalent** 80 liters water + add 960 grams Antiscalent 55% (i.e 3.3 LPH) stroke rate **Sodium Hydroxide** 80 liters water + 685 grams Caustic. Set the dosing rate to achieve RO II inlet pH 7.0 to 8.0.

SR. NO.	QUESTION ANSWER
32.23	**Maintenance of water system** Monthly UV Light Replaced after 7500 running hours Cartridge Filter - once in a three months. Vent Filter - once in a six months. User Point General Check Up Frequency is once in a six months.
32.24	 

SR. NO.	QUESTION ANSWER
32.25	
32.26	• Welding documentation (material certificates for pipes and fittings, FDA certificates for gaskets) Isometric drawings with weld numbers Welded seam documentation (machine protocols) Welder approval test certificate Pickling and passivation protocol Endoscopic photos Analytical certificate of inert gas   

SR. NO.	QUESTION ANSWER
32.27	**QUALIFICATION ITEMS OQ** • Calibration of measuring equipment (Pressure, temperature, conductivity) • Leak test • Operation of softener (residual hardness, regeneration) • Operation of RO plant (flow rates, conductivity) • Operation of bisulphite dosing (if required) • Function of regulating circuits in RO plant • Operation of ozone generator and ozone meter (ozone concentration) • Operation of UV unit (Ozone concentration, intensity of light) • System parameters and limit-value settings • Flow rate (Reynolds value) • Water quality (conductivity, microbiological situation, TOC)
32.28	• Gradients in distribution system • Drainability of distribution system • Inspection of electrical hardware • Emergency-off switch • Analogue inputs and outputs • Program steps disinfection softener, RO • Program steps sanitisation softener, RO, EDI, loop • Alarms • Access rights, passwords

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PHARMA BOOK

SR. NO.	QUESTION ANSWER
32.29	• Pretreatment Plant • Consisting of Feed Pump • Garnet Filter : For Sediment removal • Color & Odor removal • Regeneration tank : for RO Plant regeneration purpose 
32.30	• **R.O.** : Reverse of natural osmosis phenomenon • Induced by forcing the pure water through a semi permeable membrane with the help of high pressure pump • **Osmosis** – Diffusion of a solvent from a dilute solution through a semi permeable membrane into a more concentrate solution. 
32.31	• Capacity Of Distribution Tank-7 KL • Tow Loops Liquid & Tablet • Installed Return line Velocity , UV Intensity & conductivity Meter 

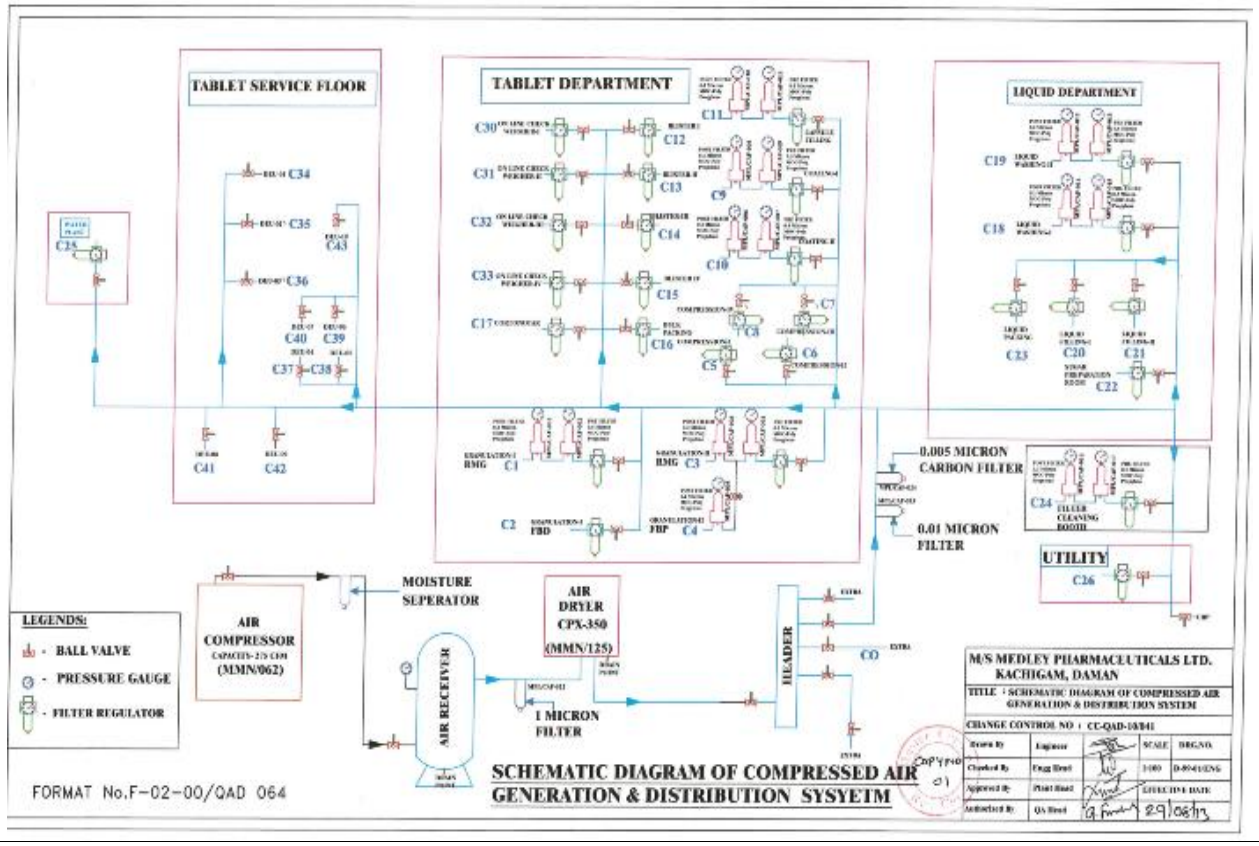
SR. NO.	QUESTION ANSWER
32.32	**WATER ANALYSIS:** **MICRO** Sterilize screw cap glass bottle of 250 ml capacity by autoclaving at 121°C and 15 lbs pressure for 30 min. Put sterilized sampling bottles, gloves, nose mask and filtered 70% IPA bottle in cleaned and dried SS sampling box and take it to sampling point. Wear gloves and nose mask. Clean the hands after wearing the hand gloves with filtered 70 % IPA solution. Open the sampling valve completely and drain 10 to 15 liter of water. Open sterile bottle and fill up to 250 ml mark close the screw cap immediately. **CHEMICAL** Rinse the bottles & stopper or cap three to four times with water. Collect the water sample approximately 650 ml) in sampling glass bottle. Close the container with stopper. For TOC testing, collect the sample in dry and clean 100 ml of volumetric flask (previously rinse with concentrated hydrochloric acid and water).
32.33	**SANITIZATION OF PURIFIED WATER DISTRIBUTION LOOP** **PRE-START** Hot water sanitize of purified water storage distribution system is normally carried out when there is no production activity. If there is any production activity then inform the concerned production officer not to operate the user point. Check the water level in purified water distribution tank on distribution panel. It should be more than 2000 liters. There shall be two booster pump (P-3 & P-4) are available for liquid loop and booster pump (P-1 & P-2) are available for Tablet loop. For Liquid loop. If booster pump (P-3) is selected, then open valves V35 and close valves V36, V37. If booster pump (P-4) is selected, then open valves V36 and close valves V35, V37. For Tablet loop. If booster pump (P-1) is selected, then open valves V33 and close valves V34, V37. If booster pump (P-2) is selected, then open valves V34 and close valves V33, V37. Close all the user points. Open lid of purified water distribution tank and check the functioning of spray ball, Rectified it, if required.

SR. NO.	QUESTION ANSWER
	Before start up the sanitization, display board “SANITIZATION IS GOING ON” in core area. **LIQUID / TABLET LOOP** Select sanitization mode. Start the boiler to generate heat, open steam supply valve to the jacketed purified water distribution tank. Switch “ON” the pump, then water will circulate from the purified water and liquid loop. Check and record the temperature of purified water in the return loop after every 15 minutes. It should be not less then 85°C. Check and record the temperature in Annexure-I. Circulate the hot water above 85°C for 60 minutes. Stop the purified water pump. Open drain valve (V37) and drain the water. Close the drain valve (V37) and start RO-II. Collect the 2000 liters purified water into Purified water storage tank. Start the purified water pump and circulate the water through the loop. Circulate the purified water for 15 minutes. Stop the purified water pump. Open the drain valve (V37) and drain the water. Close drain valve, user points and take loop in use. Update the record the sanitization details. Frequency for sanitization is once in a week.

SR. NO.	QUESTION ANSWER
	RO MEMBRANE **PRE START** Select “Manual” Mode. Ensure valve V3, V5 are open and valve V4, V6, V7 are close. Switch “ON” the booster pump (Raw water pump) by pressing START button. Collect the 300 liters of raw water in cleaning tank. Connect one end of hosepipe at the outlet of cleaning tank after 5 micron cartridge filter and another end to the inlet side of reject line of RO system with the help of clamp. Connect one end to the inlet side of reject line of RO and another end to the cleaning tank. **PRE-START** Select RO I on “Manual” mode. Ensure valve V3, V7, V15 are open and valve V4, V5, V6, V13, V14 are close. Connect the one end of hosepipe at the outlet of drain valve V15 and another end to the cleaning tank. Switch on the booster pump (Raw water pump) by pressing START button. Collect the 300 liters of portable water in cleaning tank up to the level marking. Prepare 0.5 % solution of Hydrogen peroxide in cleaning tank, as per mention below. Sanitizer: Hydrogen Peroxide (30 %), Add 5 liters of 30 % hydrogen peroxide in to the cleaning tank. Ensure valve V3, V5 are open and valve V4,V6, V7 are close. Switch ON the booster pump (Raw water pump) by pressing START button. After start of pump the solution will circulate from the cleaning tank to the RO membrane for 60 minutes. After 60 minutes of circulation. Stop the water pump. Then close V4, V5, V6 and open valve V7. Remove the hosepipe connection. Reconnected pipeline and then start RO system and flush the system for 30 minutes.

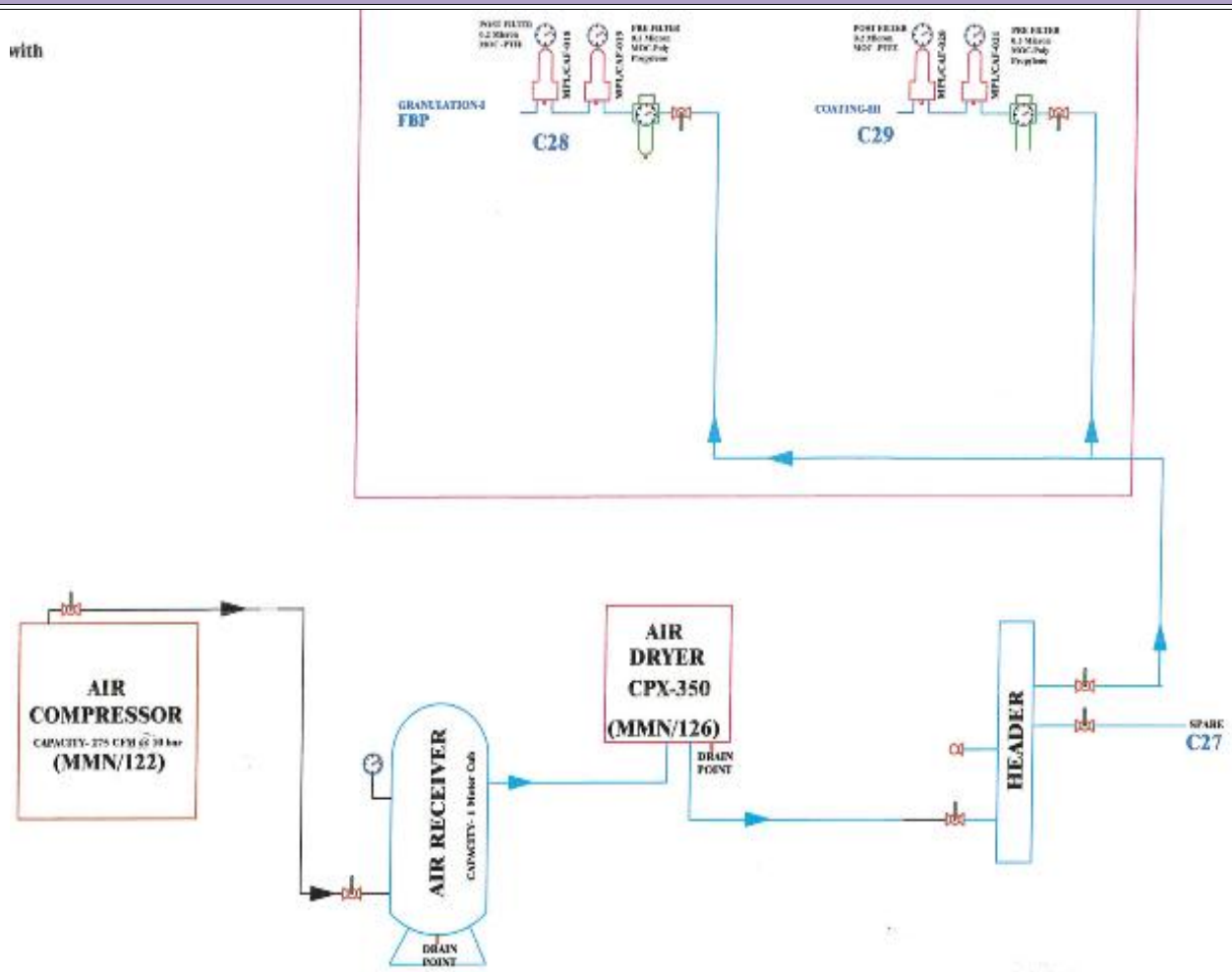
SR. NO.	QUESTION ANSWER
	Check and record the chemical consumption for RO sanitization in Annexure-II. Frequency for RO membrane sanitization is once in a fifteen days. **EDI SANITIZATION** Start RO-II and open valve (V32) to collect water in hot water tank. Switch on heater by pressing START button. Ensure that valve V28, V29, V30 & V31 is open. When temperature will reach at 75°C, Switch ON the booster pump by pressing START button. After start of pump the water will circulate from the Electro de-ionization unit and hot water tank. After 30 minutes of circulation. Stop the booster pump. Each 10 minutes interval check and record the temperature in Annexure –III. It should be more than 75°C. Re adjust all the manual valves and then start system in operation mode. Frequency for Electro de-ionization sanitization is weekly.

PHARMA BOOK

SR. NO.	QUESTION ANSWER
33.0	**COMPRESSED AIR**
33.1	**What is compressed Air and why required** Compressed air system is designed to supply oil free (Non–lubricated) compressed air to the various use points.
33.2	**Make - Chicago Pneumatic.** Capacity - 275 CFM (2 Nos)
33.3	**General Flow** The Air compressor is required to prepare compressed air at about 6.5 Kg/cm^2 which is used in the production department as utility for equipments and as an instrument air. Atmospheric air is sucked through air suction and pass through 20 micron filter. The filtered air is feed to compressor to compress the air from atmospheric pressure to about 6.5 to 7.2 Kg/Cm^2. The compress air generated is passes through coolant to cool the compressed air which is delivered by the air compressor. Moisture gets condensed and moisture is separated out in moisture separator. The compressed air filtered through 0.5 µ and 0.2 µ filter, where the viable and non viable contamination removed. The receiver is used to store the compressed air generated by the compressor. The compress air is then passes through air dryer unit to remove moisture before sending to the plant at the user point.
33.4	

Simpal Baria

PHARMA BOOK

SR. NO.	QUESTION ANSWER
33.5	with 
33.6	 • Refrigerant type • Compressed air dryer • For removal of moisture from air. • Cap. 275 CFM • moisture can remove by drain valve auto or • Level type.

SR. NO.	QUESTION ANSWER
33.7	**Test** In house validation was performed for Microbial test. Analysis for specific parameters i.e. CO, CO2, NO/NO2, SO2, Oil mist, Water Vapour, Dew point Non viable particle count test were performed by External agency.
33.8	**Method for Dew Point Test** Dew Point test kit having following component. • Closed Glass Chamber • Condenser Pipe • Digital Thermometer Take carefully and place the dew point testing kit at sampling point. Connect the compressed air line with the air compression port of dew point testing kit. Open the compressed air line valve. Transfer the acetone in the condenser pipe. Place the thermometer probe in the condenser pipe and ensure the probe proper in the acetone solution. Slow add the dry ice in the acetone to decrees the temperature inside the condenser tube. Carefully observe the surface of condenser tube inside the glass chamber for condense of compressed air water. When observe condense on surface of condenser tube recorded the temperature which is dew point. Repeat the test for two times more on same sampling point. Note down the dew point and take average.

SR. NO.	QUESTION ANSWER
33.9	**Method for Compressed air test kit for air detector tube** **Testing parameter for detector tube of different test.** Parameter for **Water vapour** content Gastec Tube No : 6 Measuring Range : 0 to 18 mg/Ltr Sampling Volume : 100 ml Sampling Rate : 100 ml/minutes Sampling Time : 01 minutes Colour Change : Green to Purple Parameter for **oil traces.** Gastec Tube No : 109AD Measuring Range : 0.2 to 5.0 mg/m³ Sampling Volume : 20,000 ml Sampling Rate : 1 Ltr/minutes Sampling Time : 20 minutes Colour Change : Pale Red to Pale Blue Parameter for **Oxygen Content.** Gastec Tube No : 31 B La Measuring Range : 6 % to 24 % Sampling Volume : 50 ml Sampling Rate : 50 ml/minute Sampling Time : 1 minute Colour Change : Black to White Parameter for **Carbon Dioxide.** Gastec Tube No : 2LC Measuring Range : 200 to 3000 ppm Sampling Volume : 150 ml Sampling Rate : 100 ml/minute Sampling Time : 1.5 minute Colour Change : Pale Blue to Purple

SR. NO.	QUESTION ANSWER

Parameter for **Carbon Monoxide.**

Gastec Tube No	:	1LC
Measuring Range	:	5 to 50 ppm
Sampling Volume	:	300 ml
Sampling Rate	:	100 ml/minute
Sampling Time	:	3 minute
Colour Change	:	Yellow to Dark Brown

Parameter for **Nitric oxide and Nitrogen Dioxide.**

Gastec Tube No	:	11 L
Measuring Range	:	0.2 to 0.5 ppm
Sampling Volume	:	200 ml
Sampling Rate	:	100 ml/minute
Sampling Time	:	2 minute
Colour Change	:	White to Yellowish Orange

Parameter for **Sulfer Dioxide.**

Gastec Tube No	:	5 La
Measuring Range	:	2 to 30 ppm
Sampling Volume	:	200 ml
Sampling Rate	:	100 ml/minute
Sampling Time	:	2 minute
Colour Change	:	Blue to Yellow

Compressed air testing kit is having following component.

- Compressed air connection port.
- Compressed air pressure controller regulator to control the pressure of compressed air at compressor air inlet.
- Pressure gauge.
- Air flow meter with regulator
- Air detector tube holder pipe.
- Stop watch.

All components are permanently adhered to SS plate except stop watch.

Take carefully and place the testing kit at sampling point where the quality of compressed air to be tested.

Connect the compressed air line with the air connection port of compressed air testing kit.

SR. NO.	QUESTION ANSWER
	Open the compressed air valve to control the required pressure of compressed air at compressed air inlet. Maintain the required air pressure by air pressure controller valve. Set the air pressure (2 Kg/cm²) by using the air pressure controller regulator. Set the air flow by using the air flow meter with regulator as per requirement of test (See detector tube literature) Break the detector tube from the both end and place the detector tube in tube holder pipe. Connect the holder pipe with detector tube at outlet of flow meter. Start the stop watch for take reading of time as per test requirement. Remove the gas detector tube from outlet of flow meter after completion of sampling. Check and record the reading on gas detector tube for reference. Mark the observation on the detector tube for reference. **Method for Total Microbial Count (TMC)** **Test for bioload (by membrane filtration method)** Media used: Soyabean casein digest broth. (Transfer 100 ml of SCDB in a 250 ml conical flask cover the pipette ends with aluminium foil and sterilize. Preparation of SCDA plates. **Equipments.** Conical flask 250 ml capacity. Flow meter. Membrane filtration unit with sterile 0.22 um membrane filter. **Sampling Procedure.** Only trained and evaluated personnel should collect the samples. Precaution to be taken by the microbiologist while connecting inlet of compressed air to the sterile flask. Nose mask and gloves to be worn. Carry the flask in respective areas. External surfaces of all sampling points are to be sprayed with 70 % v/v IPA

SR. NO.	QUESTION ANSWER
	Connect the sterile flow meter tubing's to compressed air sampling pre-determined points. Carefully insert the outlet of flow meter in to the flask containing broth. Set the flow rate 50 Ltrs/minute and bubble the air for 20 minute so as to sample 1,000 liters of air. On completion of sampling remove the tubing from the flask and cover the ends with aluminium foil. Identify each flask with proper status label indicating sampling point, sampling date and bring to the microbiology department. **Method of testing.** Test to be carried out in clean room under laminar flow only. Use filter cone with membrane filter and transfer the sample from the conical flaskto the filter holder. Follow the membrane filtration technique. After completion of filtration remove the membrane filter using sterile forceps and place it on pre-incubated SCDA plate. Incubate the inverted plate at 30ºC to 35ºC for 72 hours. At the end of incubation count the number of colonies. Calculate the TAMC/1,000 Ltrs of compressed air. If any microbial growth is there after incubation identify the colonies morphologically. **Limits:** Using autoclaved media prepare negative controls for each days testing. Growth promotion test to be performed for positive control. TAMC/1000 LTS OF COMPRESED AIR NMT 5 CFU.

PHARMA BOOK

SR. NO.	QUESTION ANSWER

AIR COMPRESSOR

- Make-Chicago pneumatic
- Capacity-275 CFM

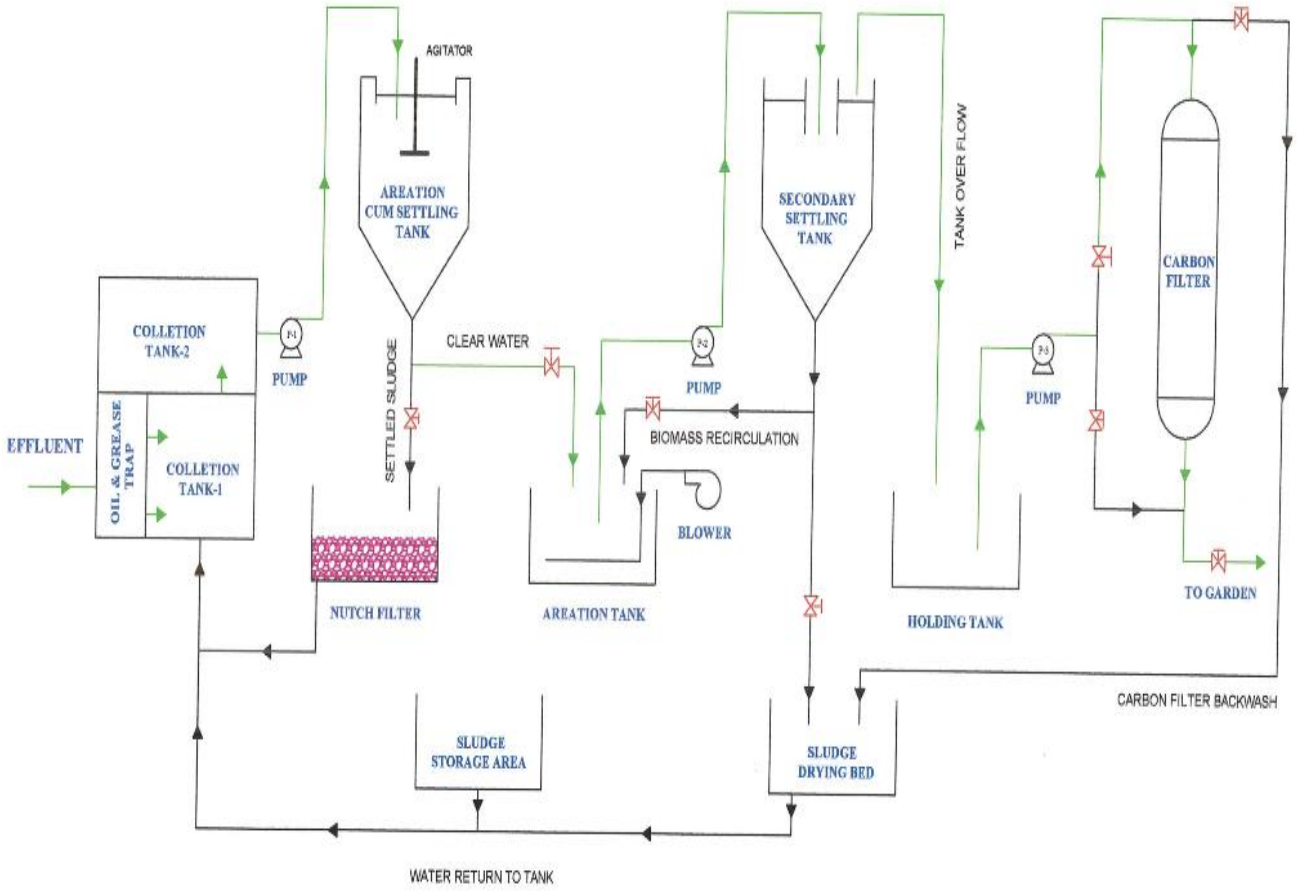


MOISTURE RECEIVER TANK

- Compressed air storage tank
- Capacity -500 Ltrs.
- With automatic drain
- Valve to remove moisture in air.



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SR. NO.	QUESTION ANSWER
34.0	**ENGINEERING**
34.1	**ETP:**  Primary Settling- Organic / Inorganic chemical separation Aeration – Biomass degradation takes place in presence of pseudonyms bacteria & oxygen Secondary Settling – Separation of addition suspended solid & biomass takes place. Mixed Bed – Color & odor removal.

Simpal Baria

SR. NO.	QUESTION ANSWER
34.2	**ELECRICAL**

POLE STRUCTURE

Taking 11 KV Power supply from Damn Electricity Board . With CTPT unit Having Dropped out fuse And ON-OFF provision Thru. Handle provided.



VACUUM CIRCUIT BREAKER

- Capacity –11 kv
- Statutory req. for HT installation & safety of Transformer & prevents Earth fault & over current in HT line.



PHARMA BOOK

SR. NO.	QUESTION ANSWER

TRANSFORMER



- Capacity: 1000 KVA
- Make: Pet sons
- Type of cooling ONAN
- With oil reservoir tank
- Manual tap changer

PANEL ROOM

- Main Incomer panel
- DG incomer panel
- Feeders for Lighting,
- ACB-4 Nos



PHARMA BOOK

SR. NO.	QUESTION ANSWER

DG:



Make :Kirloskar
Capacity: 500 & 250 KVA
Type: Radiator type
Fuel : High speed diesel
Consumption : 50Ltrs/hr.& 35 lit/hr
With accoustic enclosure
Or canopy for sound level reduction.
Use during power failure or shutdown

BOILER

Capacity : 850 kg/Hr
Fuel : Diesel
Disel Storage Tank:1 KL.
Model- RXD-850
Make-Thermax Ltd



SR. NO.	QUESTION ANSWER

CHILLER PLANT



- Capacity- 60 TR -2 No
- Application- Maintaining Temperature in area

FILTER CLEANING :

Check and Ensure that the filter cleaning equipments are clean.

Before cleaning of filters the following precaution to be Taken:

The person carrying out filter cleaning should wear the following.

* Apron
* Nose Mask
* Rubber gloves.

Start the Vacuum pump and check air is sucked from the filter cleaning bin.

Ensure that compressed air pressure should be 2.0 to 2.5 kg/cm2.

Keep the filters in filter washing bin and start cleaning the filter with filtered compressed Air & Portable water.

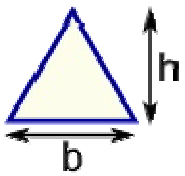
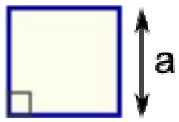
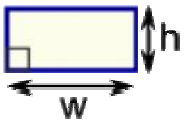
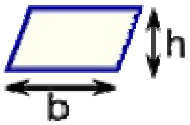
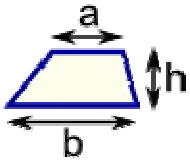
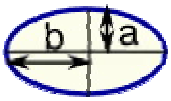
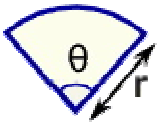
Keep the cleaned filter in infrared dryer for drying at about 80°C.

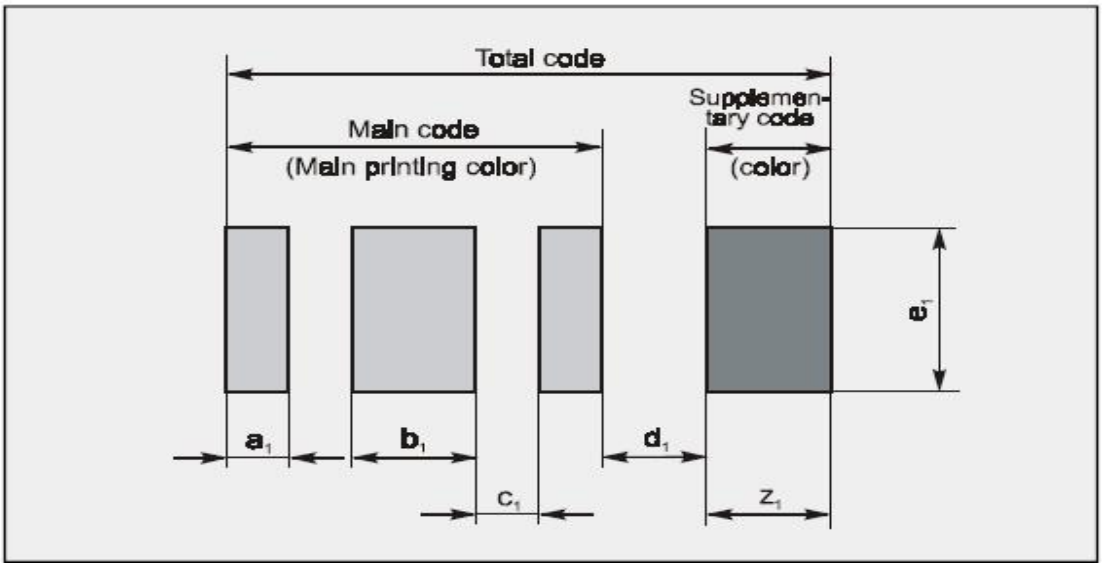
After drying, remove the filter, place it in new polythene bag and stage it on rack.

SR. NO.	QUESTION ANSWER
	STOPPING: Switch "OFF" the vacuum pump. Clean the filter cleaning bin with portable water. After drying, switch "OFF" the infrared dryer. **CLEANING OF AHU AND FDV FILTERS** Power supply to the AHU/FDV to be switch "OFF". Open the filter section door of the AHU/FDV. Ensure that the is in stop condition. Remove the filters one by one by unscrewing the filter holding clamps and put it into the clean polythene bag and tie with cable tie. Internally clean the filter section area of AHU/FDV with the Dry Cloth. Take the dirty filters from hatch for cleaning to filter cleaning room. Remove from the polythene bag and stage the filters on dirty filter rack. **10 MICRON FILTERS** Place the filter in the cleaning unit & start the vacuum pump. Clean the filter by blowing filtered compressed air in the direction opposite to the normal airflow direction. Clean the filter with potable water. Dry the filter by blowing filtered compressed air in the direction opposite to the normal air flow direction. Visually inspect the filter, if found damaged replace with new. Keep the cleaned filter in infrared dryer for drying. Chocked and requires cleaning or replacement. Clean or replace the filter as per filter cleaning SOP ENG 047 . After drying Put the cleaned filter in fresh polythene bag and transfer it to the concern area **AHU/FDV & refix the Grill / pre filter as per their respective ID No.** Close the doors of AHU/FDV and check they are locked. Start "ON "the Blower and check the AHU/FDV is running smoothly. Update the status label of the AHU/FDV unit with 'cleaned on' date & 'next due' date. Fill up the 'Record of filter cleaning 'in the Annexure-I. Frequency: Monthly / whenever Mangnehaulic gauges readings are deflated i.e. for 10 µ Limit is 2 to 15 mm of hg. **3 MICRON (MICRO-V) FILTERS** Clean the filter by blowing filtered compressed air in the direction opposite to the normal airflow direction. Visually inspect the filter, if found damaged replace with new. Put the cleaned filter with fresh polythene bag and transfer it to the concern area & refix the Grill / pre filter as per their respective ID No..

SR. NO.	QUESTION ANSWER
	Close the doors of AHU and locked. Start 'ON' the Blower and check the AHU is running smoothly. Update the status label of the AHU unit with 'cleaned on' date & 'next due' date. Fill up the 'Record of filter cleaning' in the Annexure-I. Frequency: Monthly / whenever Mangnehaulic gauges readings are deflated i.e for 3µ – limit is 2 to 12 mm of hg. **DUST EXTRACTION UNIT** Switch "OFF" the power supply to dust extraction unit Close the compressed air inlet valve of dust extraction unit Open the door of the Dust Extraction Unit. Remove the filter and put into the clean polythene bag. Collect the powder in polythene bag from bottom tray and handover to ETP for disposal. Place the filter in the cleaning bin & start the vacuum pump. Clean the filter by blowing filtered compressed air in the direction opposite to the normal airflow direction. Clean the filter with potable water. Dry the filter by blowing filtered compressed air in the direction opposite to the normal air flow direction. Keep the cleaned filter in infrared dryer for drying. Visually inspect the filter, if found damaged replace with new. Put the cleaned filter with fresh Polythene Bag in "Cleaned Filter area " and transfer to the concern Dust Collector. Cleaned the filters mounting Frame by dry cloth. After cleaning with dry cloth, cleaned with wet cloth. After properly cleaning, remove the polythene bags of filters and label & refix the cleaned filters as per respective ID no.

SR. NO.	QUESTION ANSWER
	Close the doors of dust extraction unit and check locked. Switch ON the Dust Extraction unit. Update the status label of the dust extraction unit with 'Cleaned on' date & 'Next Due' date. Fill up the 'Record of filter cleaning' in the Annexure-IV. Frequency: Weekly **RLAF/LAF FILTER** Switch "OFF" RLAF/LAF unit. Open the back door of RLAF of dispensing & sampling area / LAF of microbiology department and remove the pre-filters & intermediate filters and put into the clean polythene bag and carry to filter cleaning room. Place the filter in the cleaning bin & start the vacuum pump. Clean the filter by blowing filtered compressed air in the direction opposite to the normal airflow direction. Clean the filter with portable water. Dry the filter by blowing filtered compressed air in the direction opposite to the normal air flow direction. Keep the cleaned filter in infrared dryer for drying. Visually inspect the filter, if found damaged replace with new. Take the cleaned filter in a new polythene bag and stage on the cleaned filter rack. Put the cleaned filter with fresh polythene bag and transfer to the concern area & refix the filter as per their respective ID No. Switch "ON" Unit and Update the status label of the RLAF/LAF unit with 'Cleaned on' date & 'Next Due' date. Fill up the 'Record of filter cleaning' in the Annexure-I. Frequency: Monthly Note: Filter cleaning is being scheduled on monthly basis or depends on magnehelic gauge.

SR. NO.	QUESTION ANSWER
35.0	**PREVENTIVE MAINTENANCE**
	Maintenance means is a procedure of inspecting, testing and reconditioning a system at regular intervals according to specific instruction and, intended to prevent break down or deterioration. Preventive Maintenance shall be carried out as per respective preventive maintenance report of individual equipments Preventive Maintenance of the equipment to be carried out within ± 7 days from the schedule date otherwise deviation has to be raised.
35.1	**WHY PLANNED PREVENTIVE IS REQUIRED** ❖ PURPOSE OF PREVENTIVE MAINTENANCE: ➢ To avoid accidents & probable machine breakdowns. ➢ Reduction of the down time. ➢ Prevention of rejection during processing in order to meet the cGMP compliances. ➢ Reporting the status of deterioration of equipment to the management so that further necessa to be taken in order to prevent defects in products to meet the cGMP compliance.
36.0	**CALCULATION**
36.1	**Area = Lxw** **Volume : LxWxH** **Area of Plane Shapes**  Triangle Area = ½b × h b = base h = vertical height  Square Area = a^2 a = length of side  Rectangle Area = w × h w = width h = height  Parallelogram Area = b × h b = base h = vertical height  Trapezoid (US) Trapezium (UK) Area = ½(a+b) × h h = vertical height  Circle Area = πr^2 Circumference=2πr r = radius  Ellipse Area = πab  Sector Area = ½r^2θ r = radius θ = angle in **radians**

SR. NO.	QUESTION ANSWER
37.0	**PHARMACODE**
	Pharmacode: Pharmacode, also known as Pharmaceutical Binary Code, is a barcode standard, used in the pharmaceutical industry as a packing control system. A Pharmacode is a series of thick and thin bars, which are read using a code camera / laser scanner / single beam sensor head / packaging machine code readers for product/component security, and also serves important security system during production by avoiding any mixing of packaging materials like cartons, labels and inserts. Pharmacode numbers are used as unique security identifies on packaging material. There are two versions of Pharmacode: a one - track and two – track code. There are standard and miniature variations of the one – track Pharmacode. Miniature codes shall be used where restricted space is available (e.g. small labels, narrow carton flaps, etc.). Standard/Miniature (whichever applicable) codes shall be used for Carton and Pack inserts. However the combination of thin and thick bars will be same as that of the standard code appearing on the labels of that particular product/strength. Each component to have a unique number.
37.1	Pharmacode tolerances are checked on artwork proofs by Packaging Development and Quality Assurance Department. All Foil, Carton, Inserts and Labels used for Indian market and export market will have combination of thin and thick bars. **Standard Pharmacode:** 

Simpal Baria

SR. NO.	QUESTION ANSWER

a_1=Width of thin code bar

b_1 =Width of thick code bar

c_1=Gap between the code bars of the main code

d_1=Gap between the main code bar and the supplementary code bar

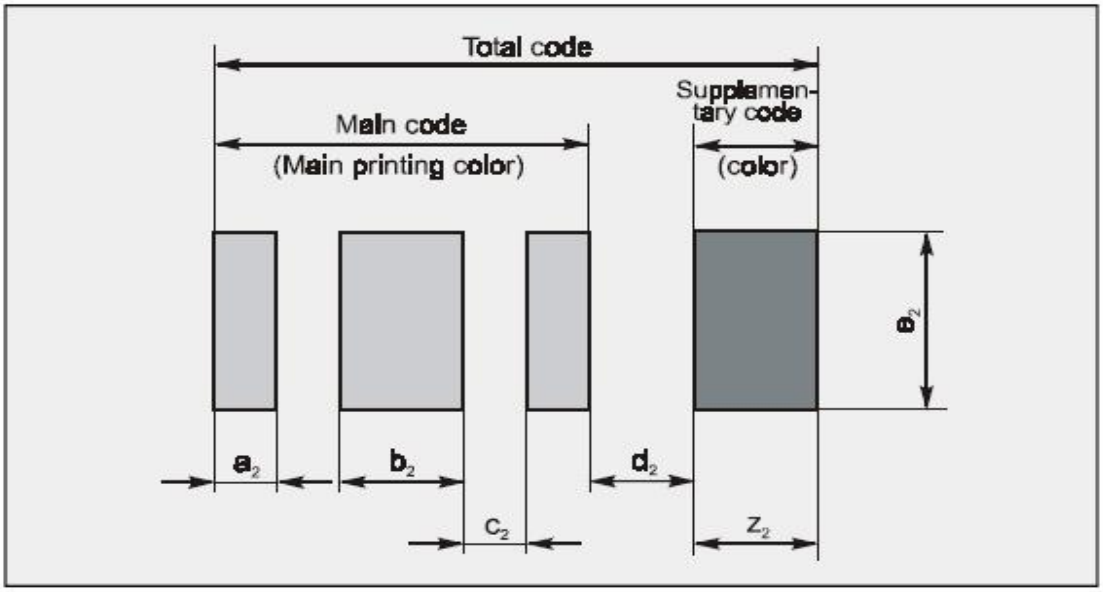
e_1=Height of code bar

z_1 =Width of colour code bar = Width b_1

.	**Standard**	**Minimum**	**Maximum**
a_1	0.5 mm	0.4 mm	0.7 mm
b_1	1.5 mm	1.3 mm	2.5 mm
c_1	1.0 mm	0.9 mm	2.5 mm
d_1	1.5 mm	1.2 mm	2.5 mm
e_1	8.0 mm	Application Specific	Application Specific
z_1	1.5 mm	1.3 mm	2.5 mm
b_1/ a_1	3	-	-

SR. NO.	QUESTION ANSWER

Miniature Pharmacode:



a_2 =Width of thin code bar

b_2 =Width of thick code bar

c_2 =Gap between the code bars of the main code

d_2 =Gap between the main code bar and the supplementary code bar

e_2 =Height of code bar

z_2 =Width of colour code bar = Width b_2

	Standard	Minimum	Maximum
a_2	0.35 mm	0.3 mm	0.45 mm
b_2	1.0 mm	0.9 mm	1.7 mm
c_2	0.65 mm	0.55 mm	1.65 mm
d_2	1.0 mm	0.8 mm	1.7 mm
e_2	6.0 mm	Application Specific	Application Specific
z_2	1.0 mm	0.9 mm	1.7 mm
b_2 / a_2	= 3	-	-

SR. NO.	QUESTION ANSWER

Calculation of Pharmacode values

Pharmacode may contain minimum 3 bars and maximum of 16 bars which are read from right to left.

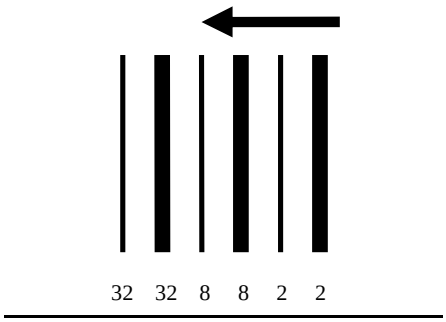
There shall be at least 1 thick and thin bar in any Pharmacode.

The values associated with each bar are summed to overall value of the code.

Minimum code value is 4 and maximum code value is 131069.

The chart is described as below.

Position	12	11	10	9	8	7	6	5	4	3	2	1
Thin bar value	2048	1024	512	256	128	64	32	16	8	4	2	1
Thick bar value	4096	2048	1024	512	256	128	64	32	16	8	4	2



Example: Pharmacode No = 32 +32+ 8 + 8 + 2 + 2 = 84

SR. NO.	QUESTION ANSWER
38.0	**SAMPLING PROCEDURE**
38.1	**SAMPLING PROCEDURE FOR IP/FG:** The total sample of blend shall be 20gm per batch per batch for in process analysis. Compressed tablets sample shall be withdrawn from container as per table No. 1.

Total nos. of containers	Nos. of containers to be sampled
1-5	All containers
6-15	Any 05 containers including first and the Last container
16 and above	$\sqrt{n}$)+1 containers including first and the Last container (n is the Total nos. of HDPE containers)

Collect sample from containers in self-sealing polybag. The total sample of tablets shall be approx 100 tablets per batch for in process analysis and shake this polybag gently to get composite sample of the entire batch.

Collect sample from containers in self-sealing polybag. The total sample of tablets / capsules shall be approx 100 units per batch

Collect the liquid syrup samples into the glass bottles from the S.S.Tank. The total sample of liquid syrup shall be 2 bottles for in process analysis.

Collect the complete pack of liquid syrup during carton packing. The total sample of liquid syrup shall be 12 bottles per batch for finished product analysis and 2 bottles from start and end of packing operation for microbial analysis.

Reserve Sample:
An appropriately identified samples representative of each lot or batch of finished drug product retained and stored consistent with product labeling

The reserve sample shall be stored in the same immediate container closure system in which the drug product is marketed or in one that has essentially the same characteristic.

Reserve samples shall be collected as a whole (complete pack) by IPQA Officer during entire run of final packing. A sticker label as "RESERVE SAMPLE" shall also be pasted on it for identification (Annexure-V) such as that it shall not hide important details on the carton (eg. Label claim, batch details, storage conditions etc.)

The quantity of reserve sample for finished product shall be twice the quantity required for the complete analysis. For Tablets and Capsules sample approximately 400 units. For Liquid orals below 50 ml pack size sample 20 bottles, for 50 ml to 100 ml sample 10 bottles and above 100 ml pack size sample 5 bottles.

Simpal Baria

SR. NO.	QUESTION ANSWER

For visual examination, the Sample quantity is as per below mentioned table

Total No. of batches manufactured	Nos. of batches to be visually inspected
1-5	All batches
6-15	Any 05 batches including first and last batch.
16 and above	(√n)+1 batches (n is the Total nos. of batches)

Samples shall be examined visually for evidence of deterioration or any physical change in the product once in a year up to the expiry.

If material is powder, capsule/tablets, it shall be immersed in half filled bucket of water and slurry shall be sent for disposal to the effluent treatment plant. If the material is liquid, it shall be diluted in half filled bucket of water and shall be sent to effluent treatment plant for disposal.

RM SAMPLING:

Raw material	Sampling device	Sample collection container
For chemical analysis	SS Spatula or SS Sampling rod.	Amber coloured glass bottle or polyethylene bag.
For microbial analysis	Sterile SS Spatula or SS Sampling rod.	Sterile amber coloured glass bottle.
Solvent	SS sampler/ Glass pipette	Amber coloured glass bottle.

For Active raw material: Draw the sample from all received containers.
For excipient,

I. All containers should be sampled if number of container are less than or equal to 5.
II. If the number of container is 5 to 16, draw the sample from 5 containers.
III. If the number of container are more than 16 number, it should be sampled by using the formula, $\sqrt{n} + 1$,
Where, n = number of container received.

For UK and USA product raw material, Active and excipient raw material sampling shall be done for all received containers (i.e.100 % sampling plan).

PACKING MATERIAL:

Number of Containers Received	Number of containers to be opened
1 to 5	All
6 to 16	5
17 & Above	√N + 1

SR. NO.	QUESTION ANSWER
39.0	**OUT OF TREND**
39.1	**Out of trend:** The data that represents abnormal pattern or behavior from normal pattern is called as Out of trend In case the results are out of trend (alert) observed in commercial batches then the same shall be investigated and report shall be closed. If required, alert values shall be revised with sound scientific justification. OOT investigation shall be closed within 30 working days from its discovery.
40.0	**EQUIPMENT CLEANING PROCEDURE**
40.1	**Type C Cleaning** **Criteria:-At the end of the shift when the same batch is to be continued on next day.** • Clean the electrical board and control panel with the help of dry lint free duster or vacuum cleaner. • Clean/wipe the outer and inner surface of the RMG with the help of dry lint free duster. • Clean the area as per the procedure for cleaning of production area, SOP No.PSG 010. • Put the status label on the machine. **Type A Cleaning** **Criteria:-1. Between batches of same product.** **2. Between batches of lower strength to higher strength of the same product.** • Ensure that the area and equipment is free from the materials, containers and documents of previous batch/product. • Clean the electrical board and control panel with the help of dry lint free duster or vacuum cleaner. • Remove the adhered material from the RMG by scrubbing with Teflon scrubber. • Clean/wipe the machine with the help of dry lint free duster. • Close the lid of the RMG. • Clean the area as per the procedure for cleaning of production area, SOP No. PSG 010. • Put the status label on the machine & area. **Type B Cleaning** **Criteria:** **1. Between batches of different product.** **2. Between batches of higher strength to lower strength of the same product.** **3. Change in colour irrespective of product and strength.** **4. After any maintenance work relating product contact part.**

SR. NO.	QUESTION ANSWER
	NOTE: **i. By any circumstances if the cleaned equipment is not used within 48 hrs then the equipment shall be cleaned as per product change over cleaning prior to use.** **ii. During continuous production/campaign production on the equipment, the equipment shall be cleaned as per product changeover cleaning after manufacturing of 10 batches or 10 days which ever is earlier** • Switch "OFF" the main power supply. • Cover the electrical boards and control panel with poly bag. • Mope the inner and outer surface & body with the help of duster and remove the adhered material from the RMG by scrubbing with Teflon scrubber. • Wash the inside RMG and outside body of RMG thoroughly with potable water. • Charge potable water into the RMG up to the height of chopper blade and operate the RMG for 2 to 3 minutes at slow speed of agitator & chopper. Stop the machine and drain the water through the discharge port. • Dismantle the chopper assembly. Remove the vent filter, main lid & gasket, small lid & gasket discharge valve and gasket and take them to the washing area. • Lift the blade of the agitator. Wash inside and outside body of RMG and agitator with 70-80 liters potable water and clean it by scrubbing with nylon scrubber dipped in 0.10% w/v of SLS solution followed by rinsing with 45-50 liters potable water till no residue of any material or surfactant is visible. • Wash the chopper assembly, vent, main lid & gasket, small lid & gasket, discharge valve & gasket with 15-20 liters potable water and clean it with 0.10% w/v of SLS solution followed by scrubbing with nylon scrubber. Rinse all the above parts with 10-15 liters potable water till no residue of any material or surfactant is visible. • Finally rinse the inside and outside body of RMG and all the dismantled parts with 55-65 liters purified water. • Collect rinse water/swab test samples and send it to the QC department for analysis. If traces found more than the permissible limit then immediately intimate to production head and QA head and address it through deviation. • Wipe out all the dismantled cleaned parts, agitator and inner surface of the body of RMG with a lint free duster dipped in 70 % v/v of IPA. • Dry all the cleaned parts, outside and inside of the body with the help of dry lint free duster or by using filtered compressed air. • Clean the electric board and control panel with dry lint free duster or by using vacuum cleaner. • Clean the area as per procedure for cleaning of production area, SOP No. PSG 010. • Remove the status label and put a "CLEANED" label on the machine and area. • Fill the area and equipment checklist and get it approved by QA after getting the results of analysis from quality control department.

SR. NO.	QUESTION ANSWER
41.0	**PUNCH AND TOOLING**
41.1	**Tip diameter of punches** • Check the tip diameter with the help of a Vernier caliper. • Check and set the zero reading of the Vernier caliper. • Place the punch tip in a vertical position. • Check the fine setting of the Vernier caliper and record the reading in the Annexure-I. • The readings should be within ± 0.1 mm of the standard dimension. **Difference in height of the punches** • Set the dial gauge of the inspection kit at zero position with the help of the standard punch height 133.60mm. • Keep the punches one by one inside the punch holder over the metal pad of the inspection kit and check the difference in deflection from the zero position. • Record the difference in Annexure I. • The difference should not be more than ±0.08 mm of the standard dimension. **Body diameter of punches** • Check the body diameter with the help of a Vernier caliper. • Check and set the zero reading of the Vernier caliper. • Check the fine setting of the Vernier caliper and record the reading in Annexure-I. • The standard dimensions and limit are as in table. **Type of tooling** | **Punch body diameter(mm)** "D" Tooling | 25.35 ± 0.1 "B" Tooling | 19.0 0.1 **Embossing of punches** Visually check the embossing & enter the remarks in the ANNEXURE I. **Difference in concentricity of punches** • Keep the punch over a 'V' block pad horizontally by keeping the magnet on and set the dial gauge at zero position over the punch body. • Rotate the punch in the clockwise direction, take two readings each from the punch (one from the top and one from the bottom of the punch body) and record the observations in Annexure I. • The deflection should be within ± 0.05 mm of the standard dimension. • Keep the punch over a 'V' block pad horizontally by keeping the magnet ON and set the dial gauge at zero position over the highest point on tip diameter. • Rotate the punch in the clockwise direction and record the observations in Annexure I. • The deflection should be within ± 0.025 mm of the standard dimension.

SR. NO.	QUESTION ANSWER

Go and No-Go of punch head.

- Take "B" or "D" type tooling "Go-No Go" punch head tester for checking punch head.
- Move the punch head through "go" side of punch head tester it should pass easily.
- Move the punch head through "no go" side of punch head tester & it should not pass through it.
- Record the observations in the ANNEXURE I.

Outer diameter of dies

- Set the dial gauge of the inspection kit at zero position with the help of the standard die master piece.
- Keep the dies horizontal position one by one over the metal pad (V BLOCK) of the inspection kit and check the outer dimension deflection from the zero position.
- Record the reading in the Annexure II. The standard dimensions and limit are as in table.

Type of tooling	Outer diameter of dies(mm)
"D" Tooling	38.10 ± 0.1
"B" Tooling	30.16 ± 0.1

Height of the die

- Set the dial gauge of the inspection kit at zero position with the help of the standard die master piece.
- Place the dies in vertical position one by one over the metal pad of the inspection kit and check the height deflection from the zero position.
- Record the reading in the Annexure II. Standard dimensions and limit are as in table:

Type of tooling	Height of dies (mm)
"D" Tooling	23.82 ± 0.1
"B" Tooling	22.22 ± 0.1

Difference in concentricity of dies

- Keep the die over a 'V' block in horizontal position and set the dial gauge at zero position over the die body.
- Rotate the die in the clockwise direction, take two readings each from the die (both side) and record the observations in Annexure II.
- The deflection should be within ± 0.05 mm.

Frequency: Inspection of punches and dies to be done after receiving of a new punch set and after compression of two million tablets per subset.

Note: Check the calibration status of dial gauge, and Vernier caliper before use and record the same as O.K. /NOT O.K. in the respective annexure. Do not carryout the inspection by using a dial gauge or Vernier caliper which is due for calibration.

SR. NO.	QUESTION ANSWER
41.2	

Tablet Tooling



- There are following types of Tooling available:
- ‘B’ -Tooling
- ‘D’ - Tooling
- ‘BB’ -Tooling
- ‘DB’ - Tooling

Type Of Tooling	Punch Diameter. (in mm)	Die Diameter. (mm)/(inch)	Punch Length (mm)/inch	Max. Tab. Size (mm) Round/Capsule
‘B’	19	30.15/ 1.187	133.60	16/19
‘D’	25.4	38.1/1.50	133.60	25/25
‘BB’	19	24/0.945	133.60	13/14
‘DB’	25.4	30.15/1.187	133.60	19/19

SR. NO.	QUESTION ANSWER

TABLE 13. CHEMICAL COMPOSITION OF TOOL STEELS

CHEMICAL ELEMENT	PERCENTAGE OF CHEMICAL ELEMENTS								
	408	S1	S5	S7	A2	D2	D3	440C	O1
CARBON	.50	.40–.55	.50–.65	.45–.55	.95–1.05	1.40–1.60	2.00–2.35	.95–1.20	.90
MANGANESE	.50	.10–.40	.60–1.00	.20–.80	.00–1.00	.00–.60	.00–.60	.00–1.00	1.20
SILICON	.25	.15–1.20	1.75–2.25	.20–1.00	.00–.50	.00–.60	.00–.60	.00–1.00	.40
CHROMIUM	.75	1.00–1.80	.00–.35	3.00–3.50	4.75–5.50	11.0–13.0	11.0–13.5	16.0–18.0	.50
VANADIUM		.15–.30	.00–.35	.00–.35	.15–.50	.00–1.10	.00–1.00		.20
TUNGSTEN		1.50–3.00					.00–1.00		.20
MOLYBDENUM		.00–.50	.20–1.35	1.30–1.80	.90–1.40	.70–1.20		.00–.75	
NICKEL	3.00							.00–.50	
COBALT						.00–1.00			

- Following definitions for direct terminology for tooling (Punches and dies).

1. **Head:** The end of the punch that guides it through the cam track of tablet machine during rotation.

2. **Head flat(Dwell Flat):** The flat area of the head that receives the compression force from rollers(in upper punches) and determines the weight and ejection height (in lower punches).

3. **Outside head Angle**: The area gets in touch with the roller prior to head flat , while compression.

4. **Inside Head Angle**:This is the area , which pulls down the lower punches after ejection and lifts the upper punches after compression.

5. **Neck:** The relived area between the head and barrel, which provides clearance for the cams.

6. **Barrel**: This area guides the punch (while going up and down) with reference to turret guides.

7. **Stem:** The area of the punch opposite the head, beginning at the tip and extending to the point where the full diameter of the barrel begins. If the chamfer is present the barrel usually reaches its full diameter just above the chamfer.

8. **Tip:** This determines size, shape & profile of the tablet.

SR. NO.	QUESTION ANSWER

9. **Tip face**: This area of punch is where the tablet is formed. Good surface finish is required here to bet quality tablets.

10. **Working length**: This distance between bottom of the cup and the head flat is called as working length which determines weight and thickness of the tablet.

11. **Overall length**: Distance between top of the cup and the head flat.

12. **Key Angle**: The relationship of the punch key to the tablet shape. The keys position is influenced by the tablet shape, take-off angle, and turret rotation.

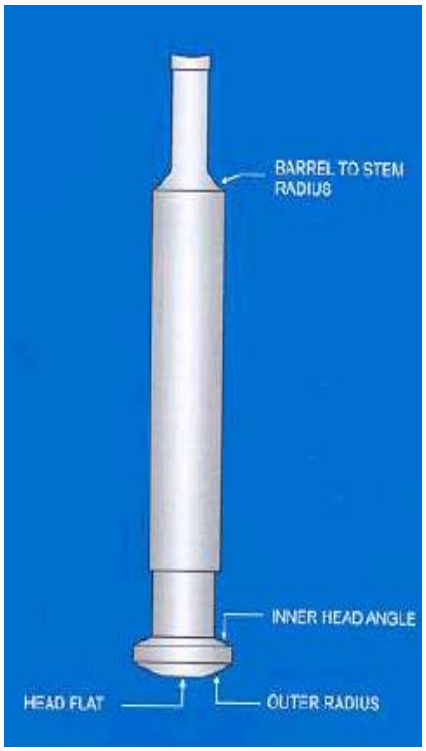
13. **Domed Heads:** Increases the dwell time and hence help to achieve the better tablet hardness.

14. **Dwell time –** The time punches spends below the pressure roller while rotating in the machine.

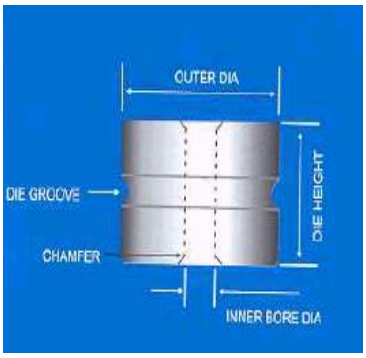
Upper Punch



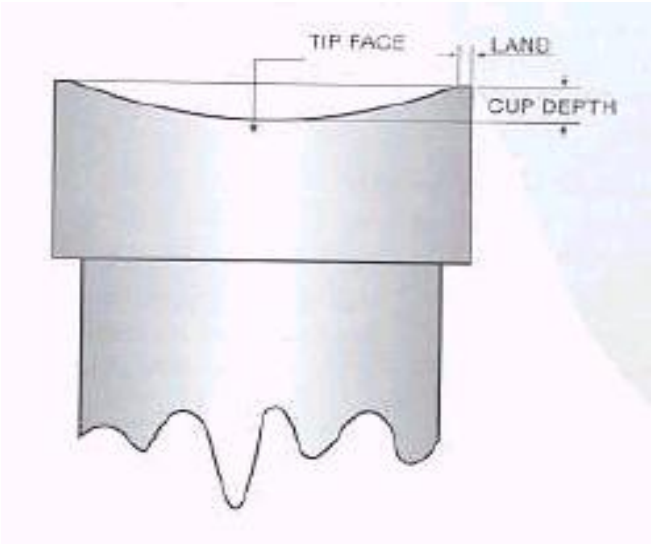
Lower Punch



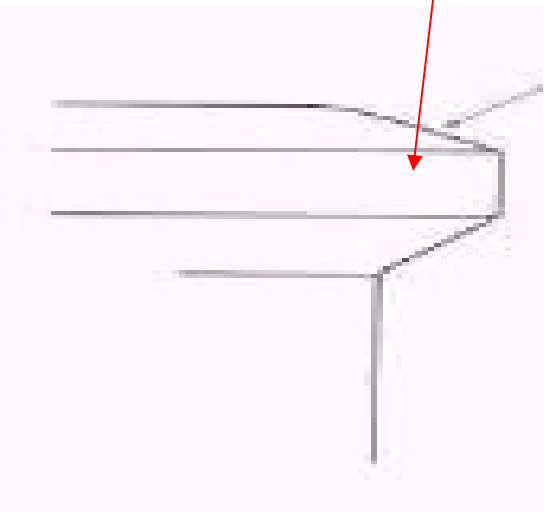
Die



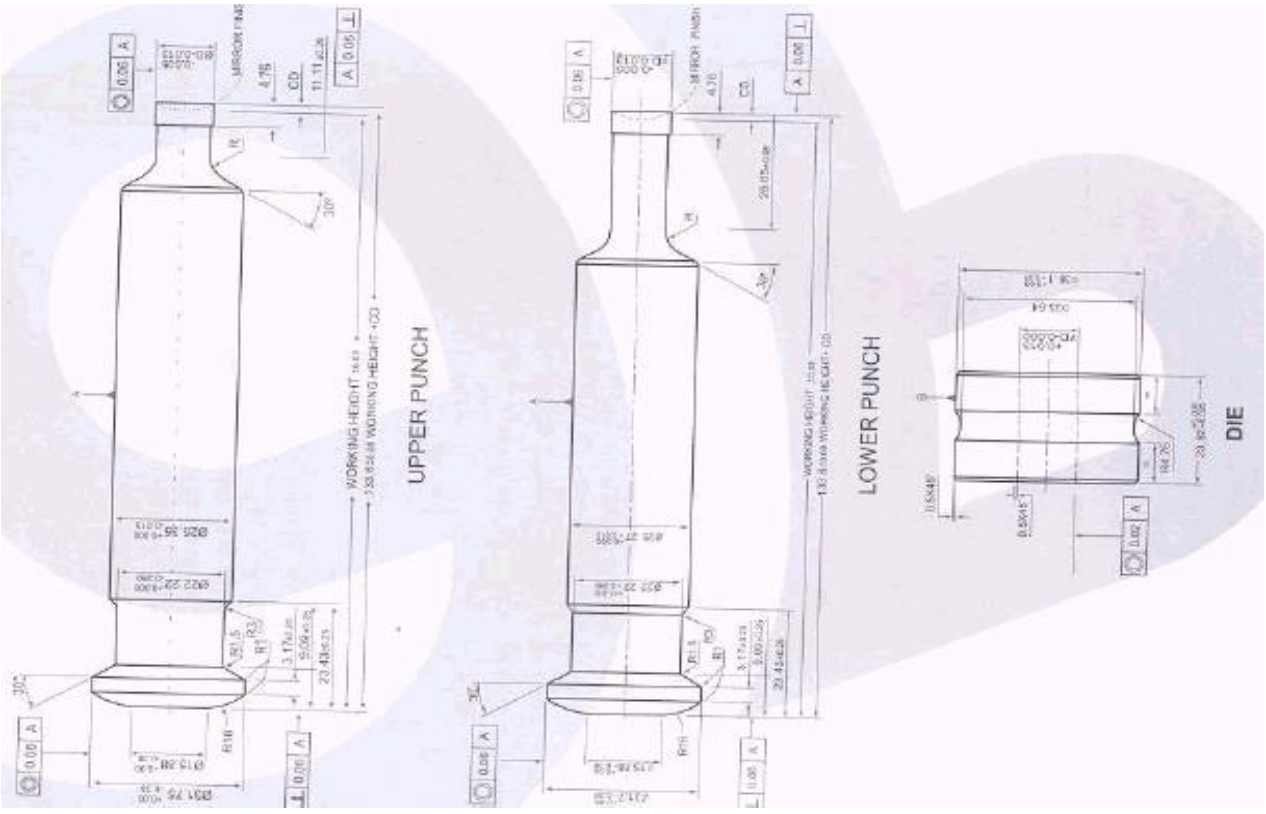
SR. NO.	QUESTION ANSWER



Radius

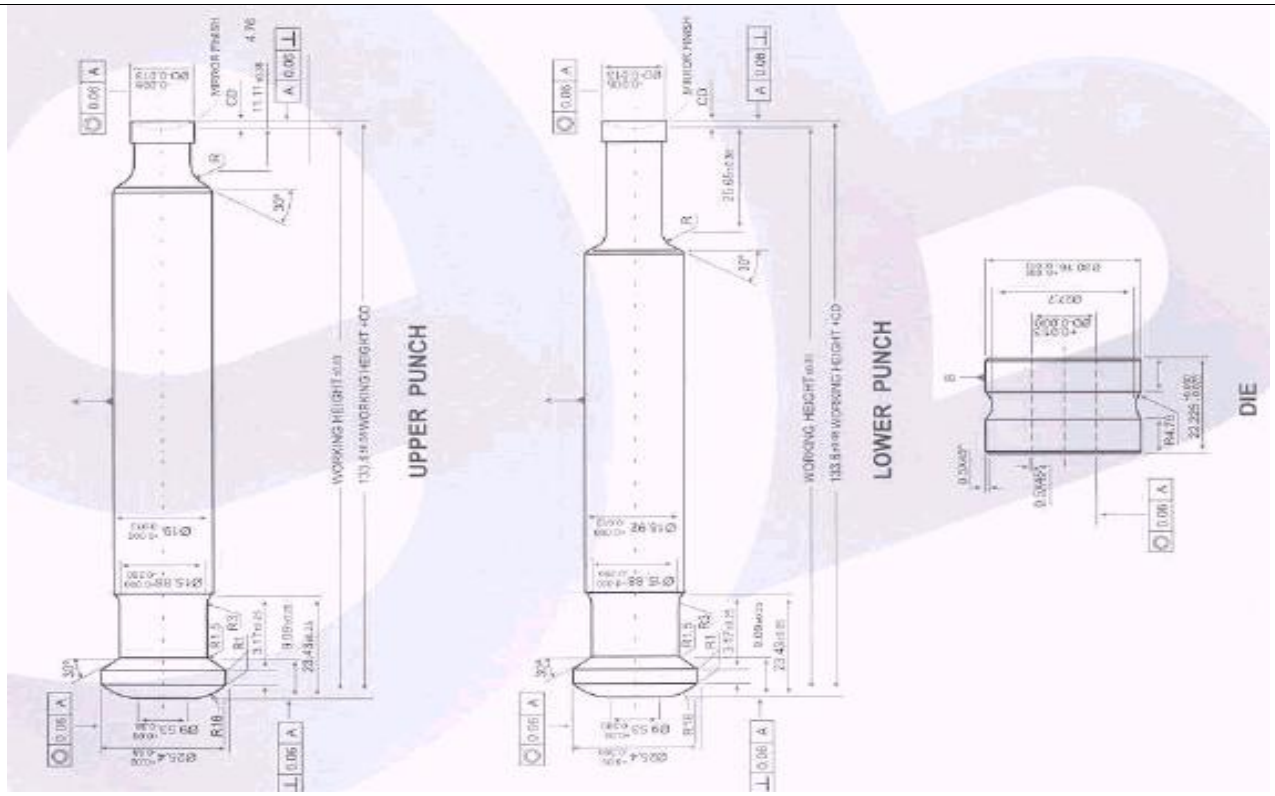


Domed head



‘D’ type tooling

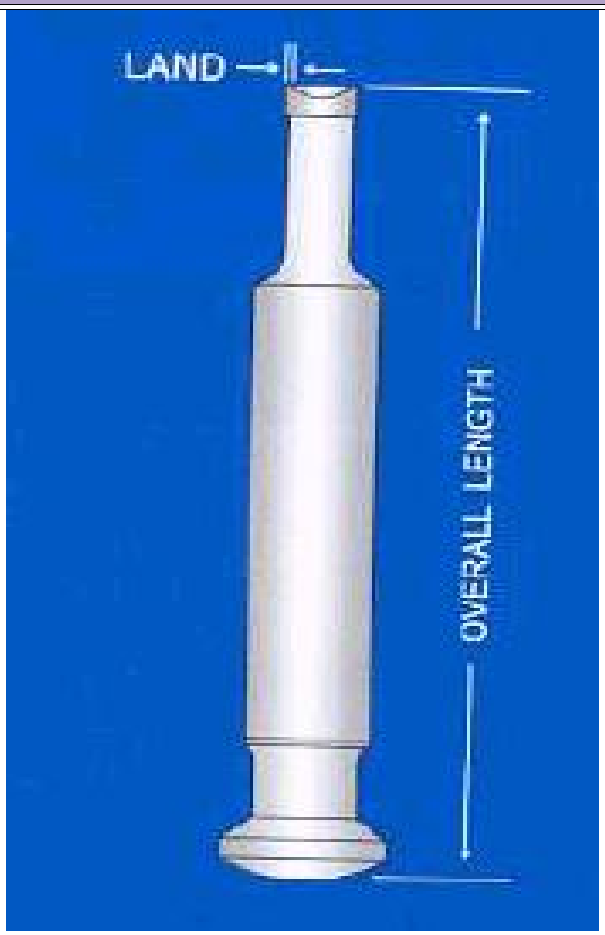
PHARMA BOOK

SR. NO.	QUESTION ANSWER
	 **'B' Type Tooling**

Simpal Baria

SR. NO.	QUESTION ANSWER





15. **Clearance**:
Die bore dia – punch tip dia = Clearance.
16. **Hardness:** Usually measured in HRC (Rockwell 'C' scale) and optimum readings are as follows:

STEEL	HARDNESS
OHNS O1	58-59
HCHC D2	59-60
HCHC D3	61-62

Normally the following combination is used.

- **For punches** **AISI O1(OHNS)**
- **For dies** **AISI D3(HCHC)**
- **Highly abrasive product punches** **AISI D2(HCHC)**

- **Die:** hardened steel (HCHC) mould to make the shape of a tablet.

Die Terminology:

1. **Die.O.D.:** The outside diameter of the die, which is compatible with the die pockets in the press.
2. **Die Height**: The overall height of the die.

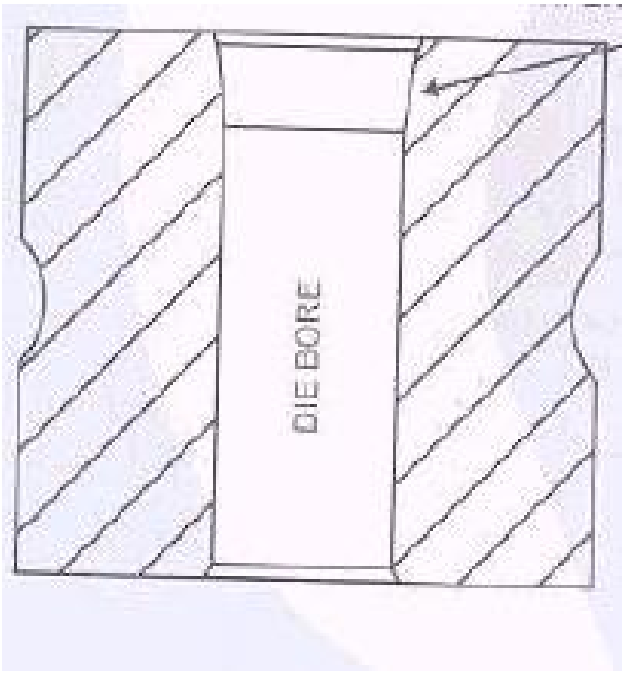
'B' Tooling-22.225 mm
'D' Tooling-23.820 mm
'BB'Tooling-22.225 mm

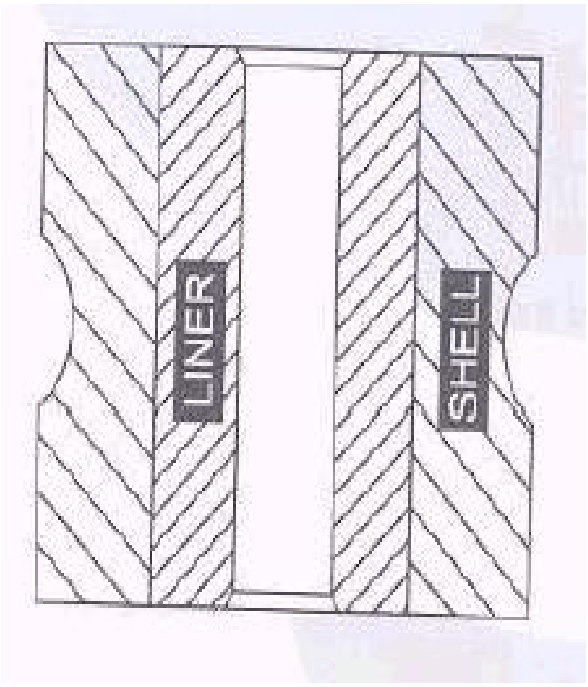
SR. NO.	QUESTION ANSWER

3. **Die Bore**: The cavity where the tablet is made. The Cavity's shape and size determine the same form of tablet.
4. **Chamfe**r: Entry angle of the die bore.

6. **Taper dies**: dies with tapered bore on one or both sides. They are used for easy ejection of tablets (mainly for double layered tablets.
7. **Die Groove:** The groove around the periphery of the die, which allows the die to be fixed in the press.
8. **Lined (Insert) Dies**: Dies fitted with a linear insert made from a much harder, more wear-resistant material such as tungsten carbide and ceramic.

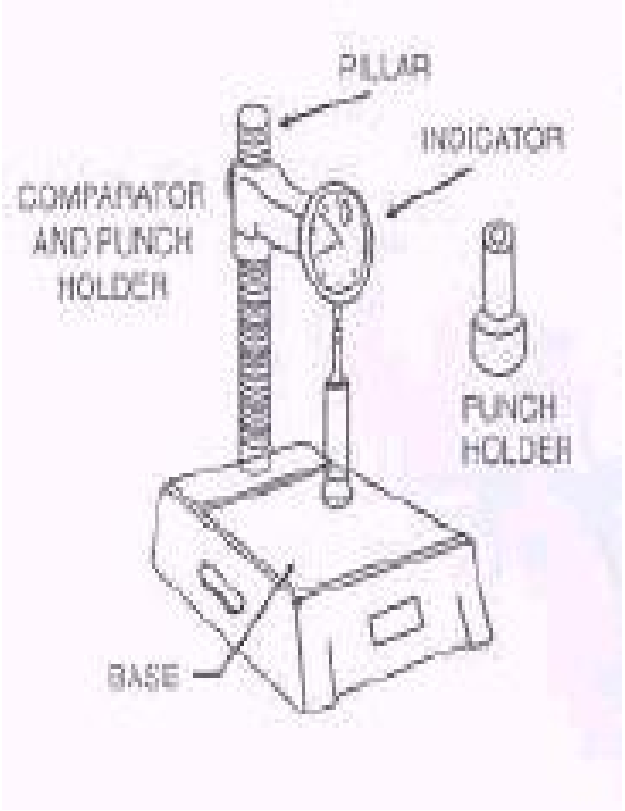
Taper in one side





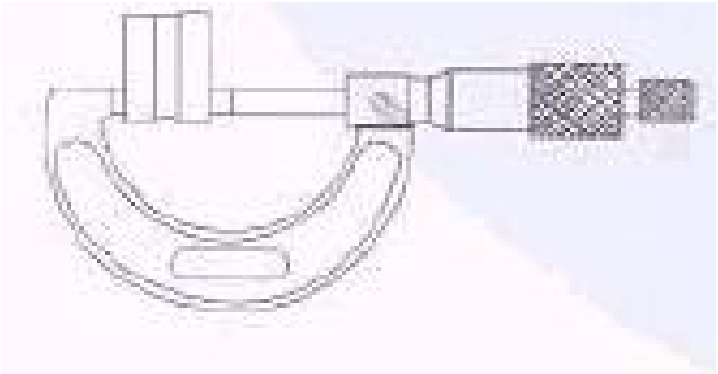
Type of product	Punch set life
Circular	**4 million tablets/set**
Other than circular	**2 million tablets/set**
Double layer	**2 million tablets/set**
Effervescent Tablet	**1 million tablets/set**

SR. NO.	QUESTION ANSWER

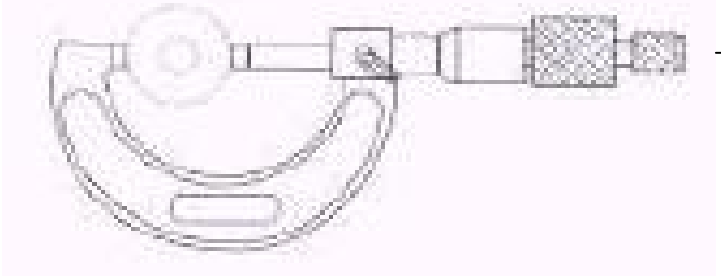




Head Inspection-
'GO' , 'NO-GO'



→ Die Height



→ Die Outer Diameter

SR. NO.	QUESTION ANSWER
42.0	**DIFFRENCE BEWTWEEN MOISTURE CONTENT AND LOD**
42.1	Know how to differentiate the moisture content or water content and loss on drying (LOD). Water content is determined by the Karl Fischer titration method and it consists of only water i.e moisture content. The results does not contain other volatile matter except the water. Loss on drying (LOD) is determined by heating the sample bellow its melting point in an oven and it includes all volatile matter including water content and solvents. Loss on Drying is an unspecific analytical technique removing not only water but all other volatile impurities like alcohol etc. from a sample. The degree of drying is dependent on, Temperature Drying time LOD or total moisture content of Pharmaceutical products can include both bound (e.g. water of hydration) & free water. In cases there are additional traces of other volatile impurities present , like alcohol ; LOD may be higher than water content. In other cases , LOD may be lower than water content, as bound crystal water may not be removed by heating. % LOD = % Water content - % water molecule in the API The Loss on Drying Test is designed to measure the amount of water and volatile matters in a sample when the sample is dried under specified conditions. e.g 105°C, 3 hours. The nature of the drug substance that is to be weighed and used in compounding a prescription must be known exactly. If the substance is a hydrate, its anhydrous equivalent weight may need to be calculated. On the other hand, if there is adsorbed moisture present that is either specified on a certificate of analysis or that is determined in the pharmacy immediately before the drug substance is used by the procedure under Loss on Drying, this information must be used when calculating the amount of drug substance that is to be weighed in order to determine the exact amount of anhydrous drug substance required.
43.0	**DIFFRENCE BEWTWEEN CALIBRATION, VALIDATION AND QUALIFICATION**
43.1	**Calibration:** The set of operations that establish, under specified conditions, the relationship between values indicated by an instrument or system for measuring (for example, weight, temperature and pH), recording, and controlling, or the values represented by a material measure, and the corresponding known values of a reference standard. Limits for acceptance of the results of measuring should be established. Always remember any reference standard is always used in calibration. **Validation:** Action of proving and documenting that any process, procedure or method actually and consistently leads to the expected result It can better understand that the validation is a documented evidence to and done to prove the consistency of the expected results of any process, procedure or method. **Qualification**: Action of proving and documenting that any premises, systems and equipment are properly installed, and/or work correctly and lead to the expected results. Qualification is often a part (the initial stage) of validation, but the individual qualification steps alone do not constitute process validation. Qualification is a part of validation.

SR. NO.	QUESTION ANSWER
43.2	**DIFFRENCE BEWTWEEN OOS AND OOS**
	of specification) is the comparison of one result versus a predetermined specification criteria while OOT (**Out of Trend**) is the comparison of many historical data values versus time. 2. OOS investigations focus on determining the truth about that one value while OOT investigations focus on understanding non-random changes. Example: The specification limit for assay is: 95.0-105.0 % w/w of label claim **Case-1:** For a particular batch, the result obtained 94.2 % w/w -This result is out of the specification limit. This is called OOS. **Case-2**: The result obtained 95.8 % w/w. Although the results are well within the specifications, we should compare the result with the previous batches trend. If we found the average value of the trend as 99.0 % w/w then this batch result (95.8%w/w) is called out of trend.
44.0	**DIFFRENCE BEWTWEEN CHANGE CONTROL AND DEVIATION**
44.1	<table><tr><th>Change Control</th><th>Deviation</th></tr><tr><td>■ It is permanent change forever.</td><td>■ It is particular change in Equip., Process, and Vendor.</td></tr><tr><td>■ Always required back up data other wise not closed.</td><td>■ Back up not required.</td></tr></table>
45.0	**DIFFRENCE BEWTWEEN SOP AND PROTOCOL**
45.1	<table><tr><td><u>SOP(s)</u> Procedures are followed in routine for consistent work performance and quality out put of the product.</td><td><u>Protocols</u> Procedures are documented for one time study to qualify or validate area/ equipment/ process/ system under study</td></tr></table>

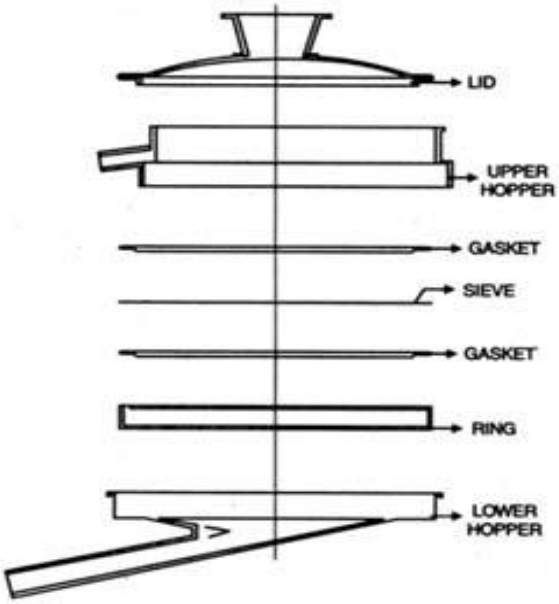
SR. NO.	QUESTION ANSWER
46.0	**CHANGE ROOM AND LINE CLEARANCE CONCEPT**
	❖ WHY CHANGE IS REQUIRED? ➢ To reduce intake of dust, dirt, microbes in the processing area. ❖ SOURCE OF DUST, DIRT & MICROBES ARE : ➢ Man ➢ Material ➢ Machine ➢ Environment ❖ What is Change Room? Buffer between clean and unclean area ❖ Clean Area : Has a provision to control dust, dirt and microbes. ❖ Unclean Area : Doesn't have any provision to control dust, dirt and microbes.
46.1	**LINE / AREA CLEARANCE** To ensure that there are no items, packaging components, residues of previous product & any other unwanted material on the line Implications ➢ GMP Violation ➢ Mix-ups ➢ Contaminations ➢ Cross contaminations ➢ Product Failure ➢ Market complaints
	CONTAMINATION, CROSS CONTAMINATION AND MIX - UP ❖ CONTAMINATION : In any product, presence of a substance other than product manufacturing formula is called contamination. ❖ CROSS CONTAMINATION : Contamination of one product to another is called cross contamination. ❖ MIX - UP : Undesirable mixing of material, product/ batch, unintentionally or accidently is called Mix-up.

SR. NO.	QUESTION ANSWER
	SOURCE — CONTAMINANT • Human Beings : Bacteria, Pathogen, Fibre, Hair, Skin fragments, Nail • Air : Bacteria, Pathogen, Dust, Gases, Fumes • Water : Bacteria, Pathogen suspended matter • Equipment & Accessories : Previous product traces, material of equipment construction, cleaning • Raw Material : Impurities, Residual solvent, Black particles etc. • Primary Packaging : Extraneous matter, Material Bacteria Pathogen
47.0	**BATCH RECORD**
47.1	**What is Batch Records?** Batch Record is a complete set of documents Containing; Full details of manufacturing & packing procedures & analytical documents. **Why Batch Record is required?** Batch Record contains Manufacturing procedures, list of Equipment to be used for manufacturing. It is the only proof for the batches manufactured and packed as per requirement dispatched. Records provide the history of each batch of the product, including its distribution and also of all other relevant information pertinent to the quality of the final product. It is also required for the investigation in root cause analysis, when ever there is any complaint received from market. It is required to register the products in different countries and regulatory authorities

SR. NO.	QUESTION ANSWER
48.0	**PASS BOX**
48.1	**TYPES OF PASS BOX** 1. Dynamic Pass Box 2. Static Pass Box **DYNAMIC PASS BOX** For Material transfer from unclassified area to classified area. This Pass box having HEPA filter and UV Light Frequency of Validation is every six month Test: 1. Air Velocity 2. Filter Integrity 3. Particle count **STATIC PASS BOX** For Material transfer from classified area to classified area.

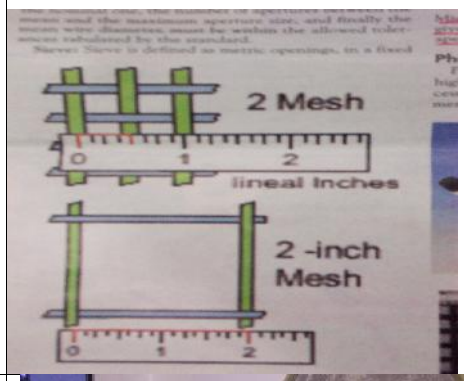
SR. NO.	QUESTION ANSWER
49.0	**EQUIPMENT AND PROCESS**
49.1	**SIFTING**  The purpose of sifting is to grade/obtain a uniform particle size powder of desired range, oversize and undersize particles are separated during this operation. The operation is carried to check for any foreign matter which may come along with the raw material. The principle of gyratory motion is, if a body is allowed to rotate at high speed around its own axis, in a plane and it is free to move in all other three planes, the gyratory forces developed are such that they tend to bring the axis of rotation of the body parallel to the axis of earth

SR. NO.	QUESTION ANSWER



- **Lid: S.S lid is with charging port to avoid spillage of powder material**
- **Upper hopper**
- **Neoprene food grade rubber gaskets**
- **Sieve**
- **Neoprene food grade rubber gaskets**
- **Ring**
- **Lower hopper**

Note: Sieve /gasket modified.



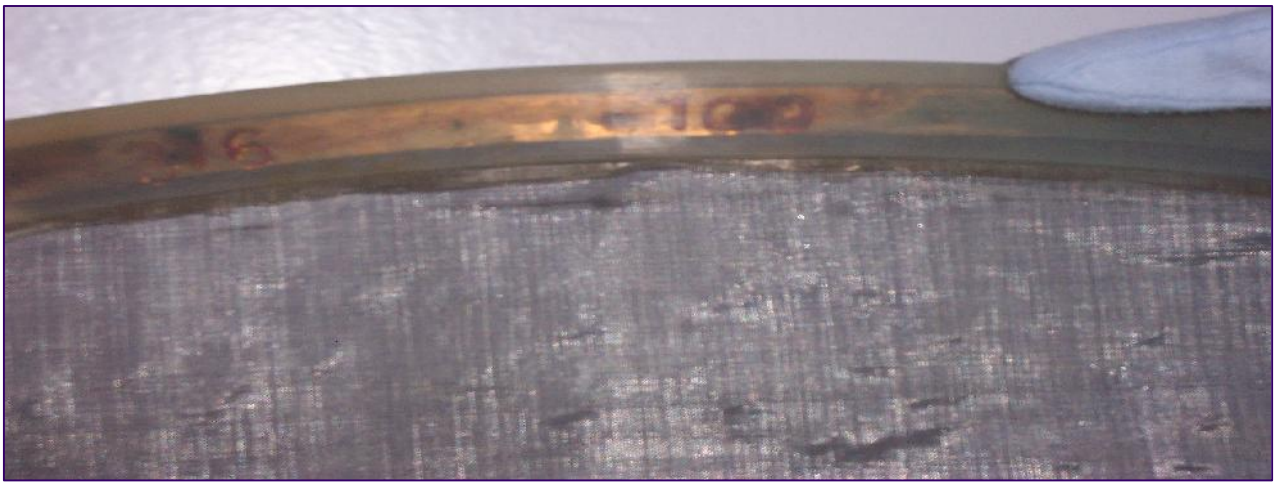
- **Efficiency of the sieving process depends on dimensional accuracy of the apertures of the sieve.**
- **Accurate way of measuring the aperture size is to measure the dimensions of individual apertures in both X and Y direction and use smallest value to give equivalent opening.**
- **In order to asses compliance of sieve with respect to standard, a substantial No. of apertures and wires through out the sieving medium must be measured.**



- **Operator has to hold the sieve against the light / Illuminations and check for any damage.**
- **Absence of any projection on surface of sieves is confirmed by gently moving the gloved hand over both the surfaces of sieve.**
- **Sieve integrity should be checked before and after sifting operation.**

SR. NO.	QUESTION ANSWER





GRANULATION

- Granulation is the process in which powder particles are made to adhere to form agglomerates called granules.

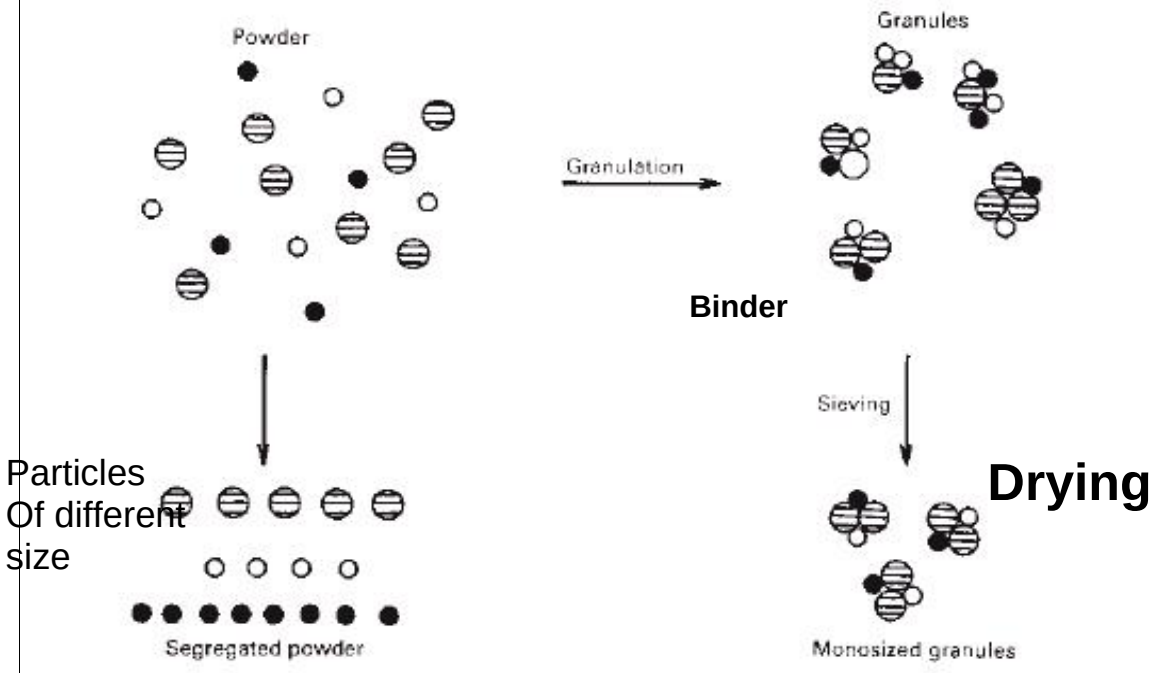
- To prevent segregation of the constituents of the mix.
- To improve the flow properties of the mix.
- To change the particle size distribution so as to improve the compressibility and to increase apparent density of the powder.

- Granulation of toxic material reduce the hazard associated with handling of toxic dust. Granulation should be non-friable & have suitable mechanical strength.
- For slightly hygroscopic material granulation reduces possibility of caking. As granules can absorb more moisture yet retain their flow ability because of their size.

SR. NO.	QUESTION ANSWER

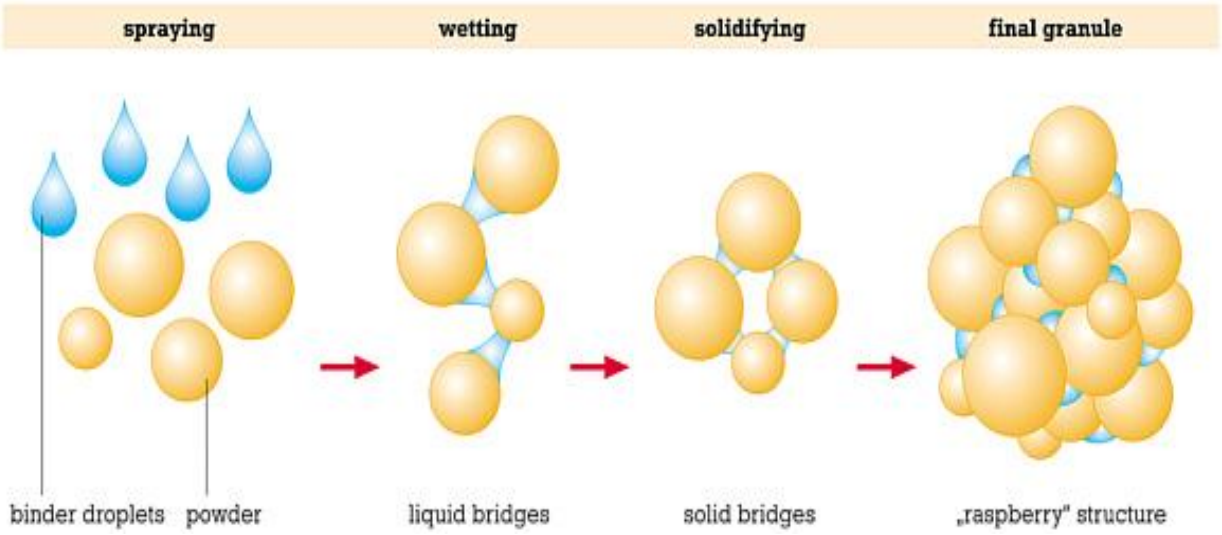
- Granules being compact than the powder occupy lesser volume per unit weight therefore they are more convenient for storage and shipment.
- Granulation can improve or modify drug release profile.

- ***Particle-bonding mechanisms***
- To form granules, physical/chemical bonds must be formed between particles so that they adhere.
- These bonds must be sufficiently strong to prevent breakdown of the granule to powder in subsequent handling operations till compression.
- There are five primary bonding mechanisms between particles.

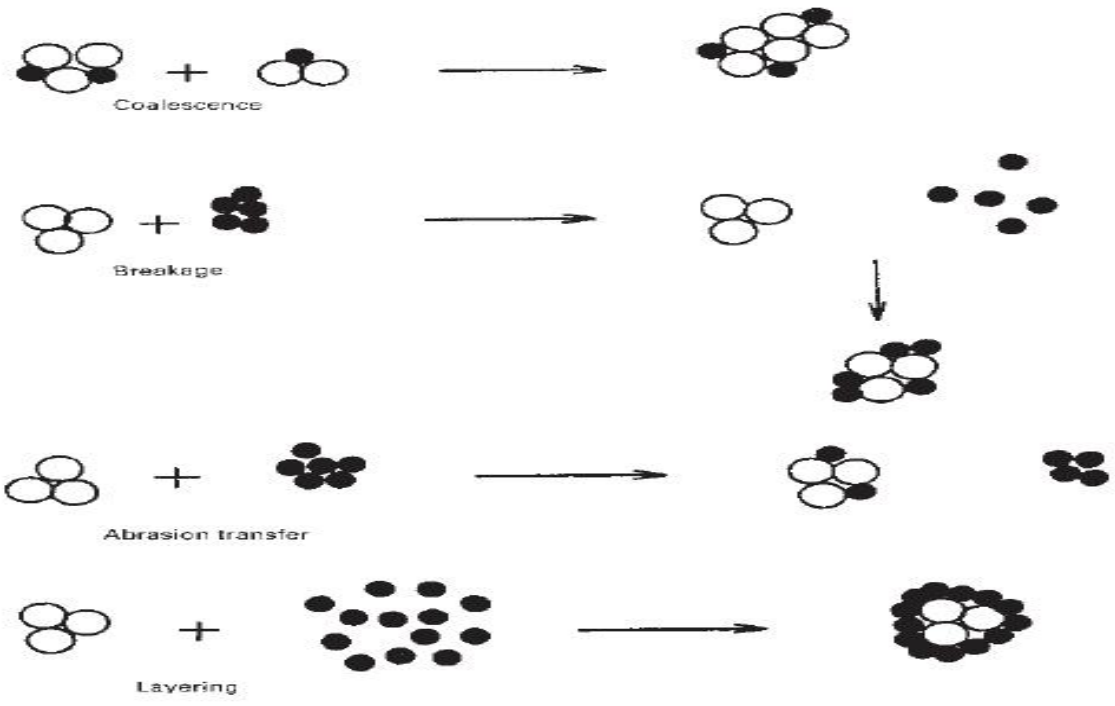


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Agglomeration



Mechanism of ball growth during granulation



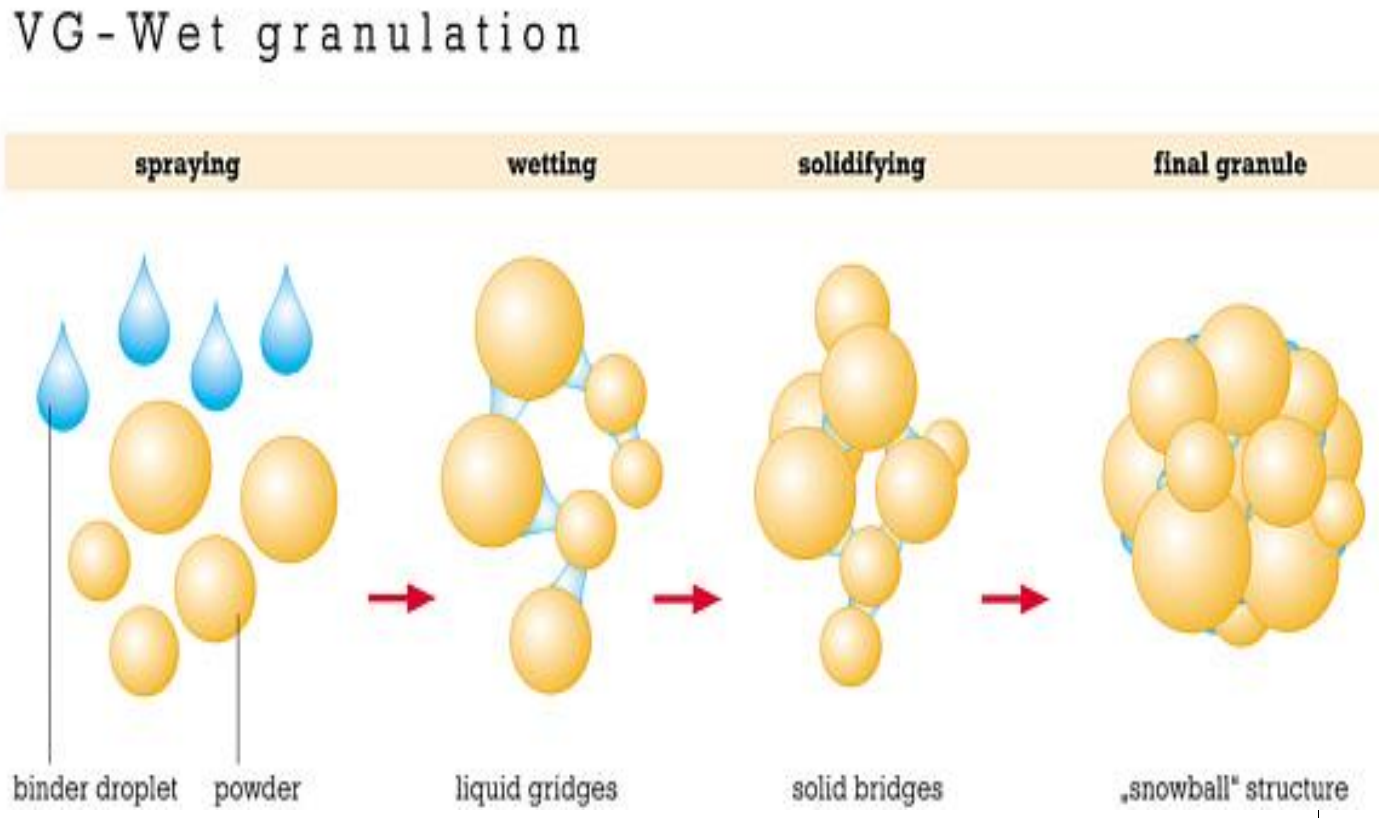
SR. NO.	QUESTION ANSWER

There are two types Methods for granulation

1. Wet granulation method: In this granulation binder solution is used.
2. Dry Granulation: Granulation is achieved with the help of mechanical compaction or force.

- Wet granulation, the process of adding a binder solution to the mix, is one of the most common method of granulation. The process can be very simple or very complex depending on the characteristics of the powders e.g Hydrophobic mix is difficult for wetting.
- Wet granulation forms by binding the powders together with an adhesive, instead of by compaction.
- The liquid plays a key role in granulation . Liquid bridges are developed between the particles and the tensile strength of bonds increases as amount of liquid added is increased.

- Wet granulation involves the massing of a mix of dry primary powder particles using a granulating fluid.The fluid contains a solvent which can be removed by drying, and should be non-toxic.
- Typical solvents include water, ethanol and isopropanol and methylene chloride either alone or in combination.
- The granulation liquid may be used alone or, more usually, as a solvent containing a dissolved binder / suspension / gelatinized binder. (also referred to as a binder or binding agent) which is used to ensure particle adhesion once the granule is dry.

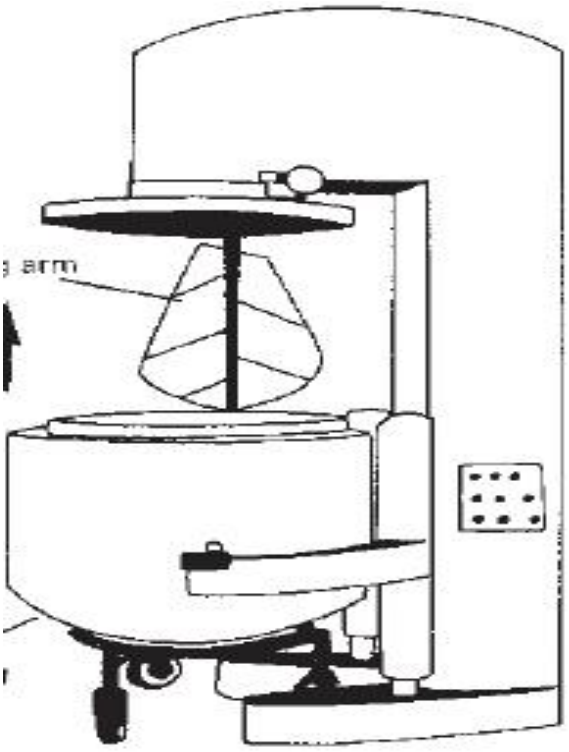


SR. NO.	QUESTION ANSWER

Wet granulation can roughly divided on the basis of manufacturing process as

- Granulation carried out using Planetary Mixer
- Granulation carried out using Rapid mixer granulator (RMG).
- Granulation carried out using single pot processor.

Planetary mixer is used for wet mixing of the powders, Powder mixing usually has to be performed as a separate operation using suitable mixing equipment. The mixed powders are fed into the bowl of the planetary mixer and granulating liquid is added as the paddle of the mixer is responsible for wet mixing and kneading action required to form the granules. The paddle of planetary mixer has planetary motion. Design of mixer is such that there is a bare minimum clearance between wall of mixer and blades and devoid of any void spaces.

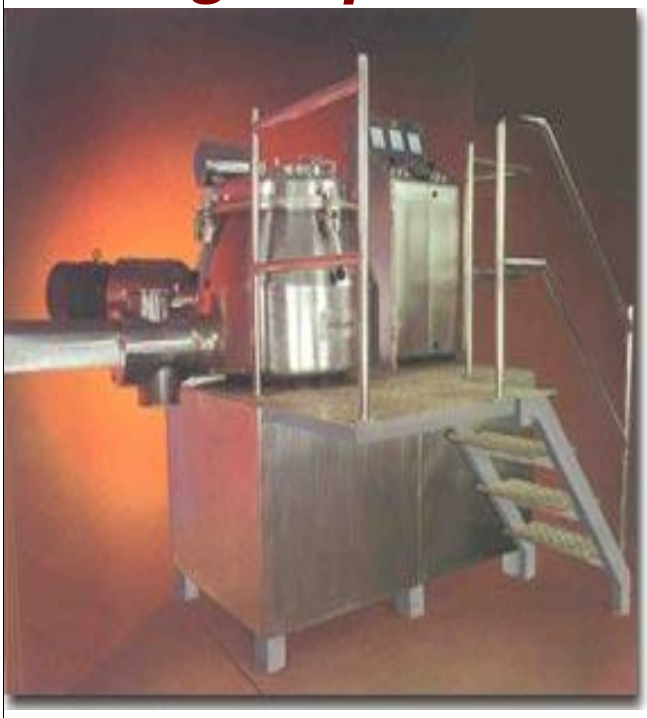


Mixing Arm.

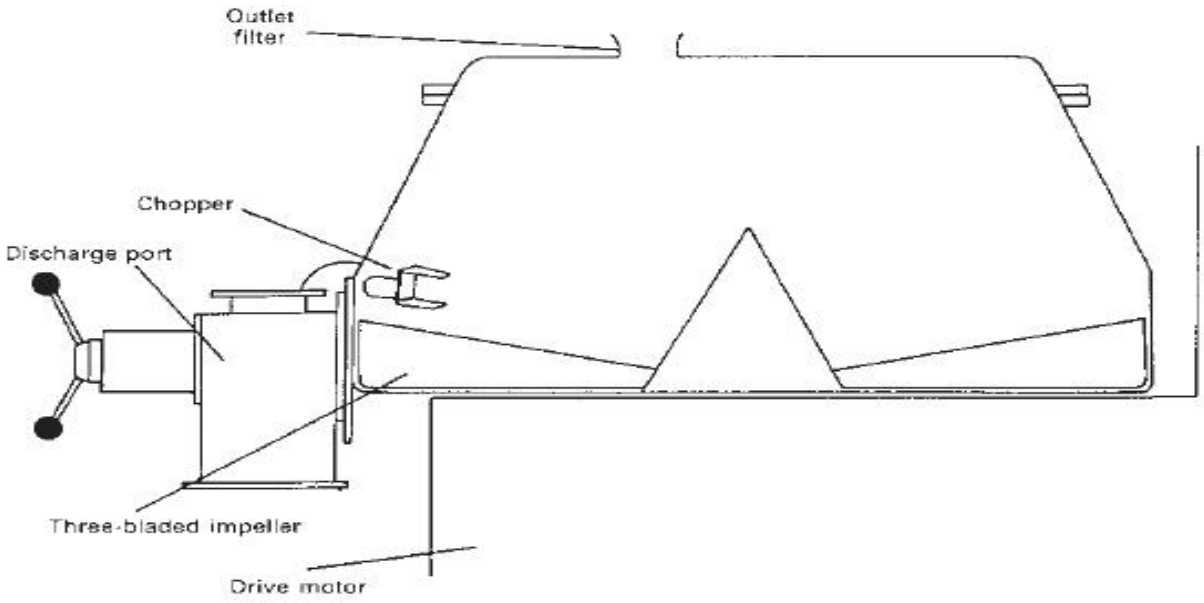
Mixing bowl is in the lowered position (This bowl is raised on the mixing arm for granulation

SR. NO.	QUESTION ANSWER

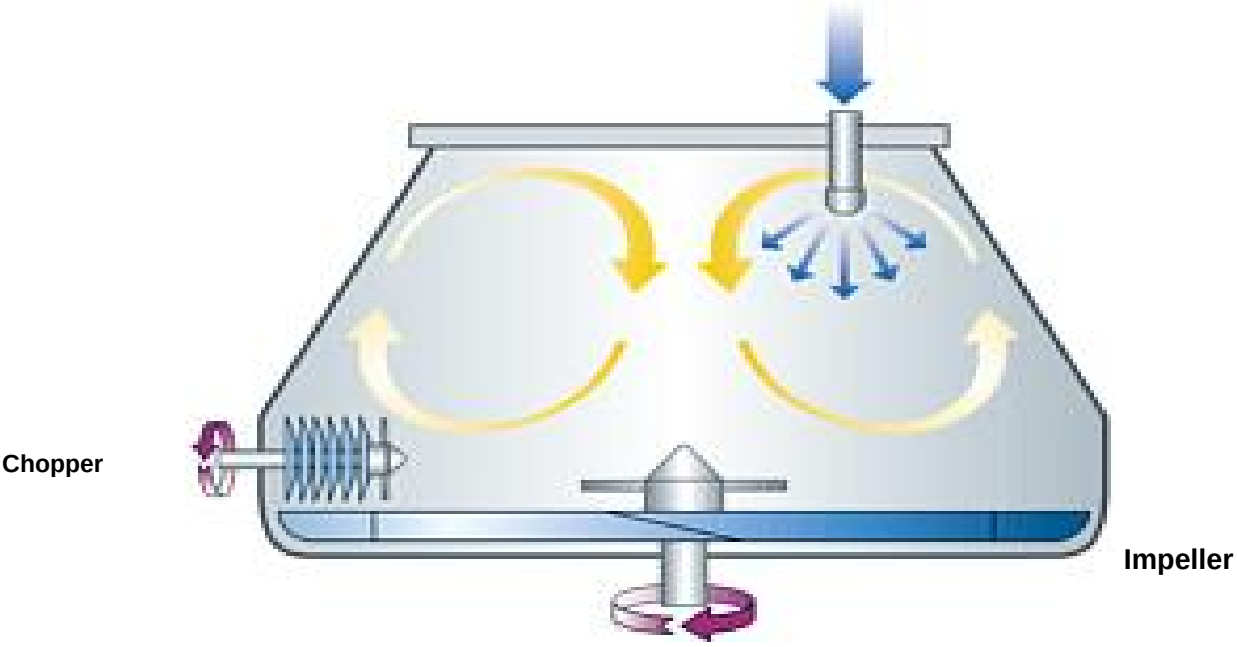
High Speed mixer/granulator



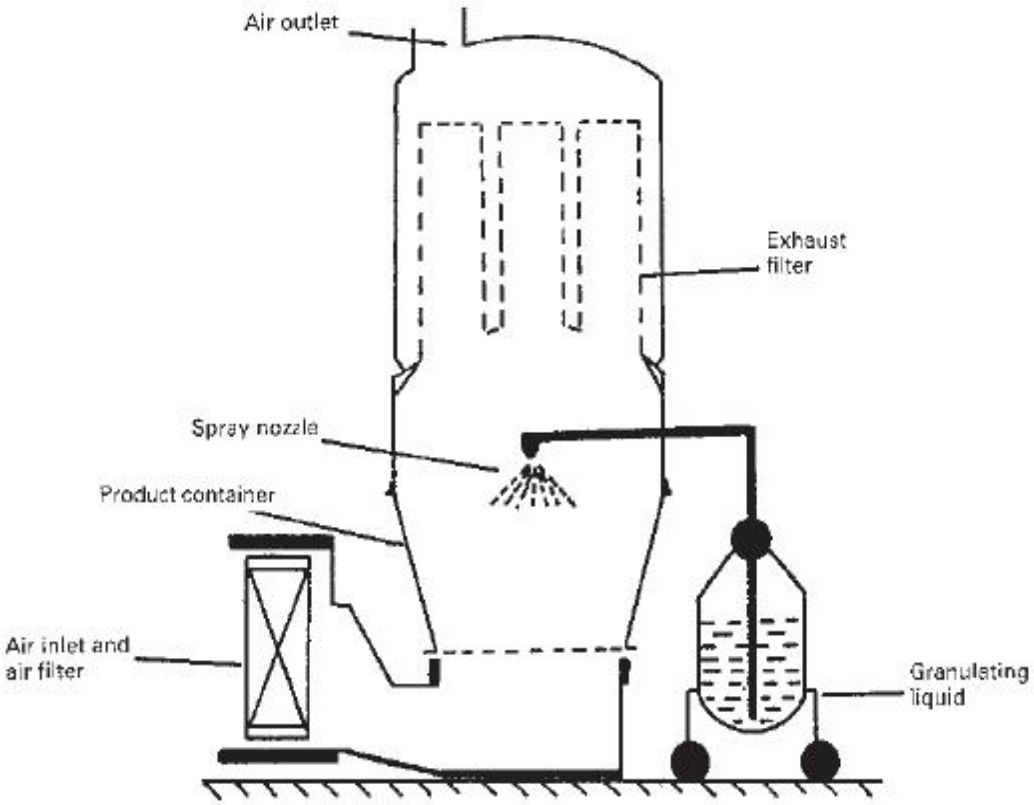
The machines have a stainless steel mixing bowl containing a main impeller, which revolves in the horizontal plane, and a auxiliary chopper (breaker blade) which revolves either in the vertical or the horizontal plane.



SR. NO.	QUESTION ANSWER



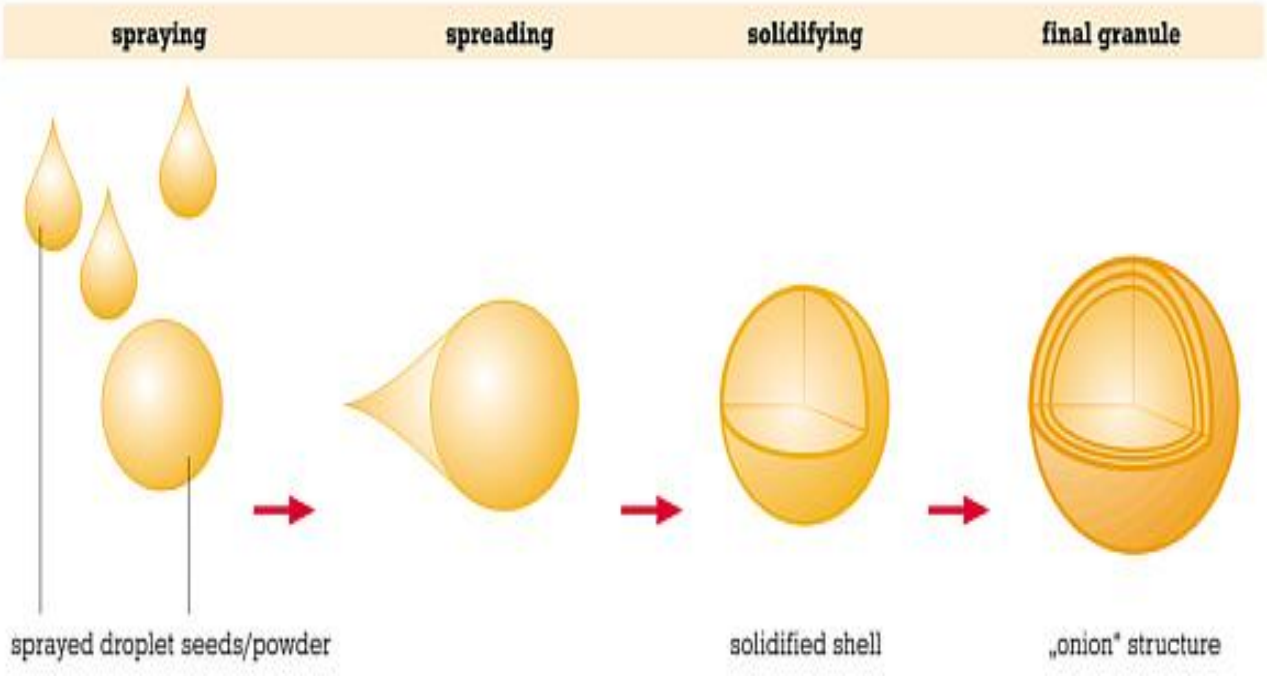
Fluidized Bed Granulator



Simpal Baria

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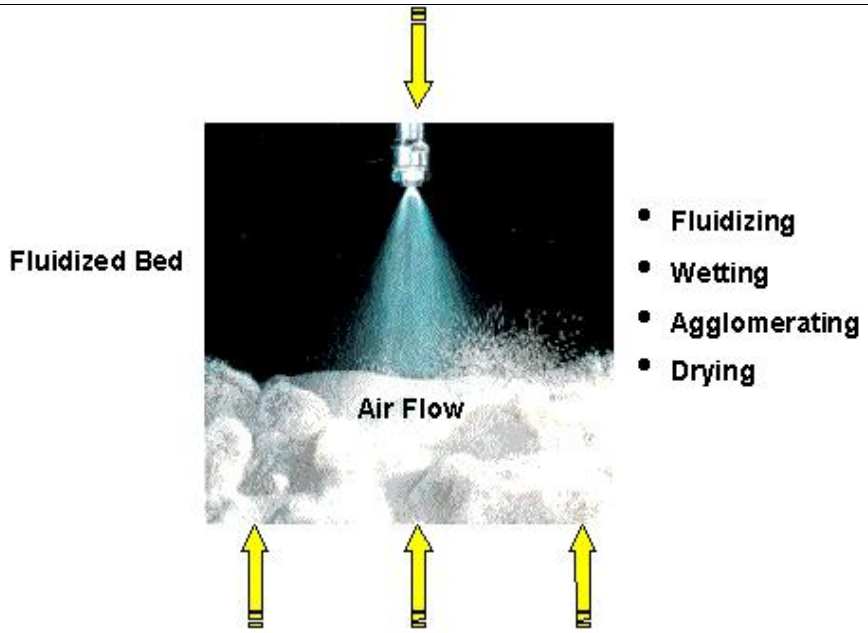
Spray granulation

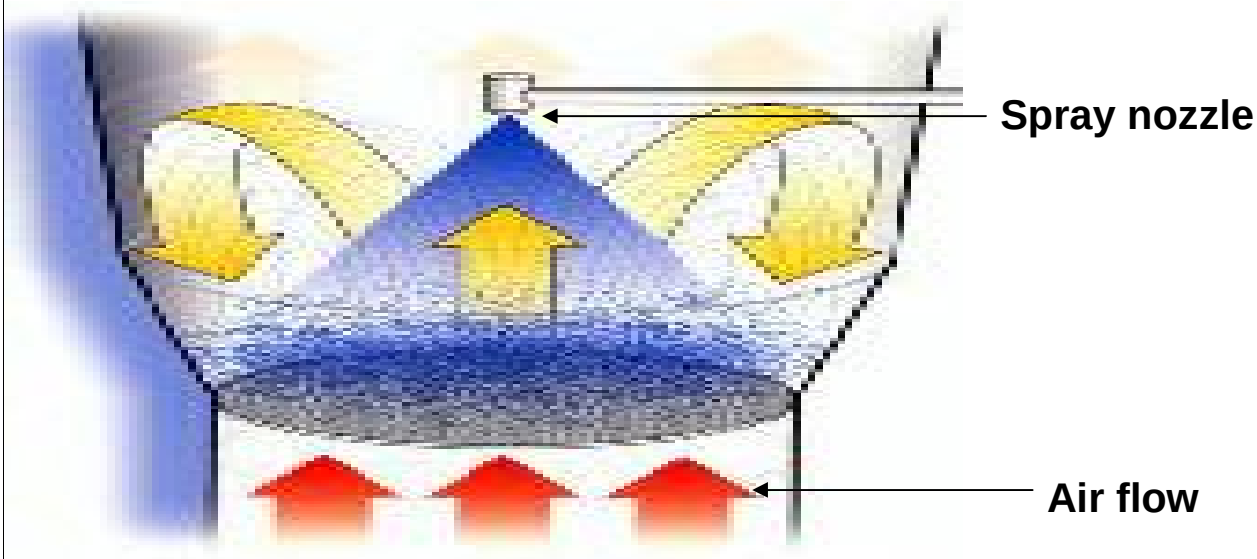


- Spray granulation is the drying of liquid (solution, suspension, melt) while simultaneously building particle size.
- Mixing an active ingredient with a carrier in the liquid phase the active will be encapsulated in a matrix of carrier after the spray granulation. process.
- Seeds for the granulation can be charged into the granulator (external seeds) or they are formed within the fluid bed by abrasion (internal seeds). The sprayed liquid is coating the seeds and is dried.
- Doing this again and again onion-like granules are formed.

- Fluidized-bed granulators have a similar design and operation to fluidized-bed driers. The powder particles are fluidized in a stream of air, but in addition granulation fluid is sprayed from a nozzle on to the bed of powder.
- Granulating fluid is heated and filtered air is blown or sucked through the bed of unmixed powder to fluidize the particles and mix the powder; fluidization is actually a very efficient mixing process. pumped from a reservoir through a spray nozzle positioned over the bed of particles.
- The fluid causes the primary powder particles to adhere when the droplets and powders collide.

SR. NO.	QUESTION ANSWER





Advantage of Fluid bed Granulator.

- Rapid wet massing, agglomeration and drying is carried out in within one unit.
- Granulation operation are less laborious and time consuming as compared to other types of wet granulators.

Disadvantages of Fluid bed Granulator.

- No adequate mixing of powder components.
- There is tendency of demixing especially when there is disparities in particle size and density in the material being processed.
- Particles under granulation has tendency to stick to the equipment filters this reduces effective filter surface area. This also cause product loss and increase in cleanup difficulties.

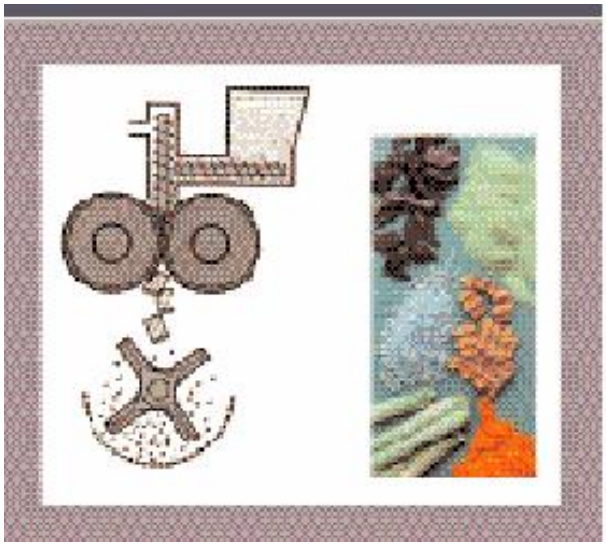
SR. NO.	QUESTION ANSWER

- Generally water is used as solvent as it is economical, but in case of some drugs water may adversely affect drug stability, causing hydrolysis of susceptible products, and even it needs a longer drying time than organic solvents do.
- This increases the length of the process and again may affect stability because of the extended exposure to heat.
- Occasionally non aqueous solvents or solutions that are composed of water or water miscible solvents are used to improve the granulation properties of formulation.
- Whenever non aqueous solvents are used in granulation reduced amount of energy is required for drying.
- This gives requirement of proper ventilation and safety precautions against Fire, toxicity and explosion

Dry Granulation

- The dry granulation process is used to form granules without using a liquid solution because the product to be granulated may be sensitive to moisture and heat.
- Forming granules without moisture requires compacting and densifying the powders.

Dry granulation can be conducted on a tablet press using slugging tooling or on a roller compactor commonly referred to as a When a tablet press is used for dry granulation, the powders may not possess enough natural flow to feed the product uniformly into the die cavity



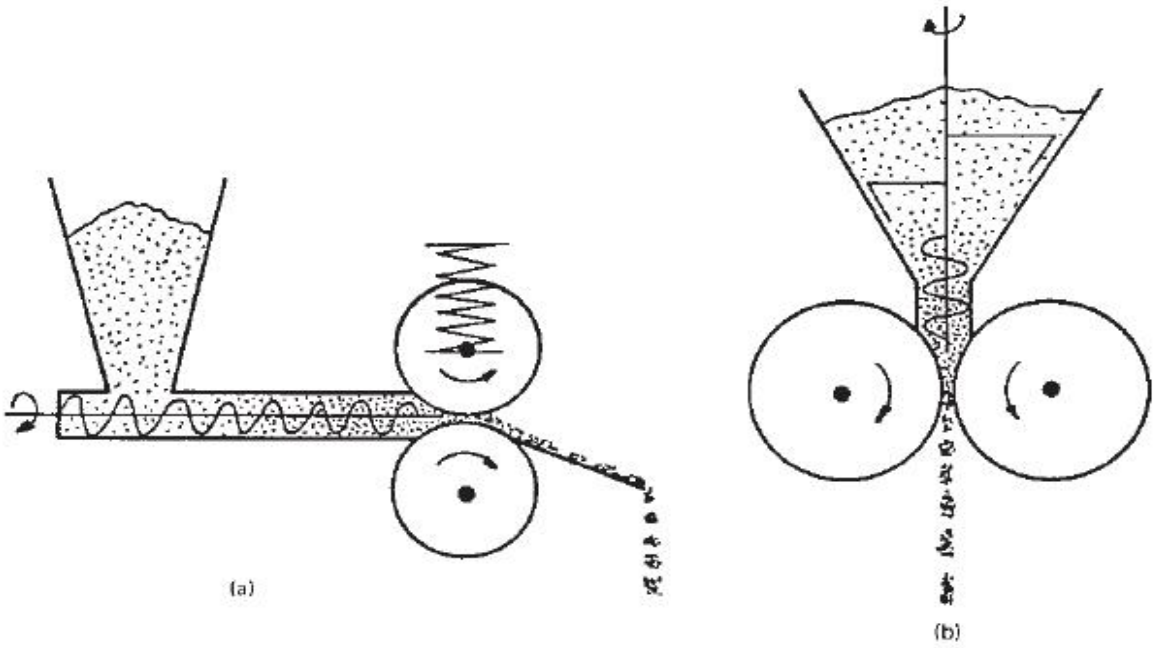
The dry granulation process is used to form granules without using a liquid solution because the product to be granulated may be sensitive to moisture and heat. Forming granules without moisture requires compacting and densifying the powders.

- ***Sluggers:***
- The dry powders can be compressed using a conventional tablet machine or, more usually, a large heavy-duty rotary press can be used.
- This process is often known as ‘slugging’, the compact made in the process (typically 25 mm diameter by about 10–15 mm thick) being termed a ‘slug’.
- A hammer mill is suitable for breaking the compacts.

SR. NO.	QUESTION ANSWER

- **Roller compactors:**
- Roller compaction is an alternative gentler method, the powder mix being squeezed between two rollers to form a compressed sheet.
- The sheet normally is weak and brittle and breaks immediately into flakes.
- These flakes need gentler treatment to break them into granules.
- This can further be milled in to desired particle size.

Dry Granulation (Roller compactor)



To determine End point of granulation.

Granulation is rather Art than science. There are following ways to determine the granulation end point.

- To make a ball of granules in fist by applying little pressure. The resultant ball should not be too hard or soft. It should break after applying little pressure. The remains after breaking of ball should be granules and not fines.
- To measure the amperage.
- To measure the torque.
- Under granulated batch: This batch will have more percentage of fines. This will result into flow problem.

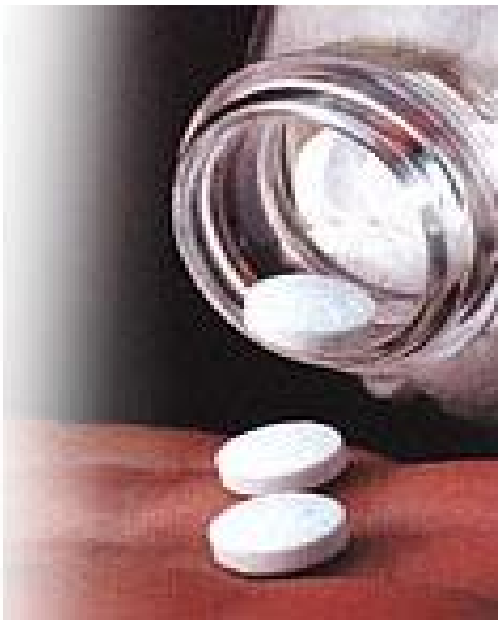
This batch may have capping, chipping, ejection and hardness problem.

- Over Granulated batch may have uneven distribution of fines, hardness and compressibility problem.

This batch may have uneven colour distribution, DT and dissolution problem.

SR. NO.	QUESTION ANSWER

Tablets



• Drug substances are frequently administered orally by means of solid dosage forms such as,Granulates, Tablets and Capsules.

Definition of Tablets

Tablets can be defined as Solid Pharmaceutical Dosage form containing drug substances with or without suitable diluents and prepare either by compression or molding methods.

- There are various types of Tablets and abbreviations used in referring them are as follows.

1. Compressed Tablets (CT)
2. Sugar-Coated Tablets (SCT)
3. Film-Coated Tablets (FCT)
4. Enteric-Coated Tablets (ECT)
5. Multiple Compressed tablets (MCT)

5.1 Layered Tablets, 5.2 Press-Coated Tablets.

6. Controlled Release tablets.
7. Tablets for Solution / Dispersible Tablets.
8. Effervescent tablets.
9. Compressed Suppositories or inserts.
10. Buccal and Sublingual Tablets.
11. Vaginal tablets.
12. Lozenges.
13. Implants.

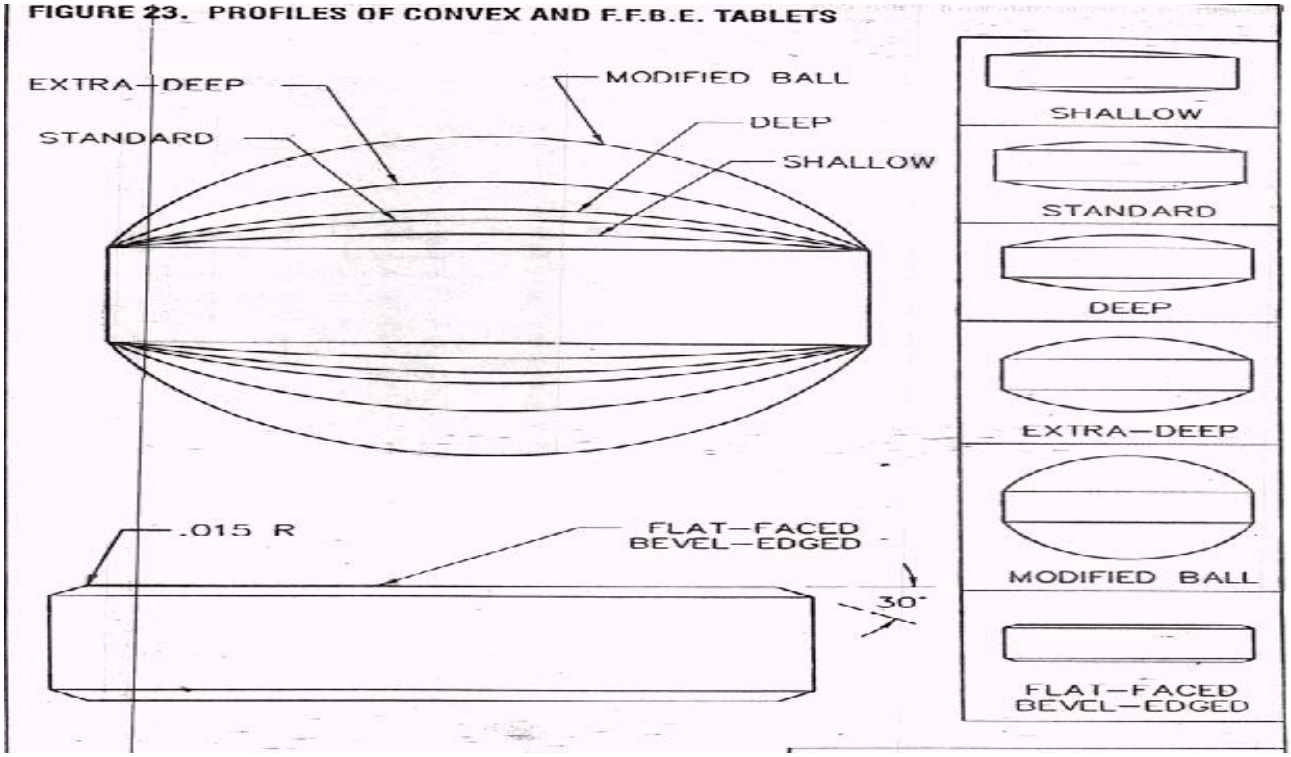
Tablet Tooling

For this purpose different types of punches are used:

- Flat- faced bevel- edged.
- Shallow concave (Round/ Capsule shaped)
- Standard concave (Round/ Capsule shaped)

SR. NO.	QUESTION ANSWER

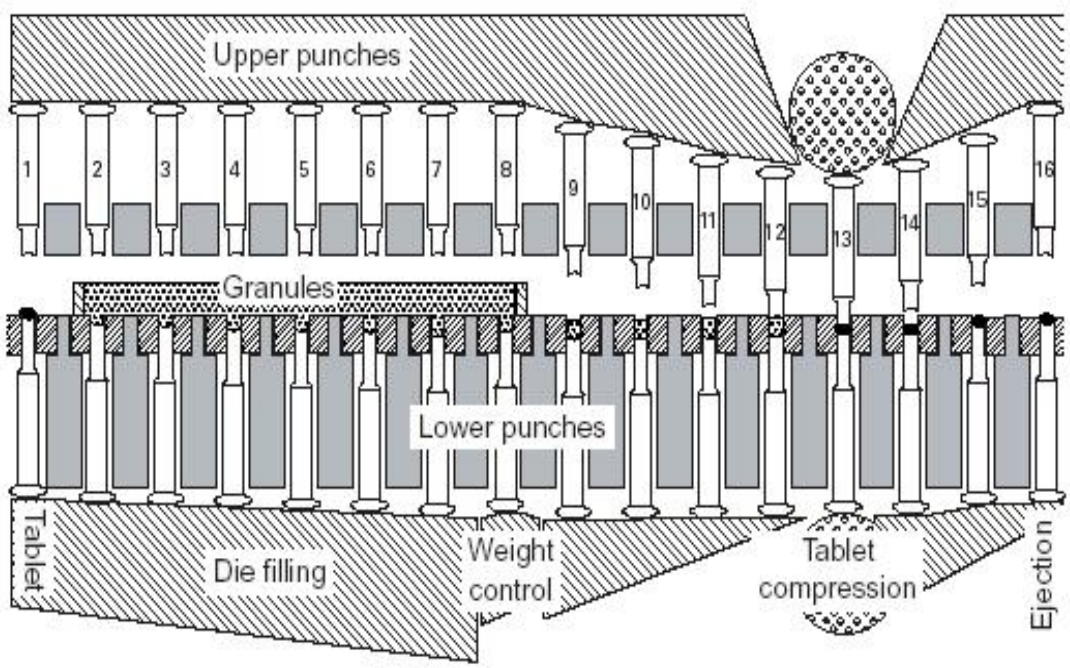
- Deep concave (Round/ Capsule shaped)
- Extra deep.
- Modified ball

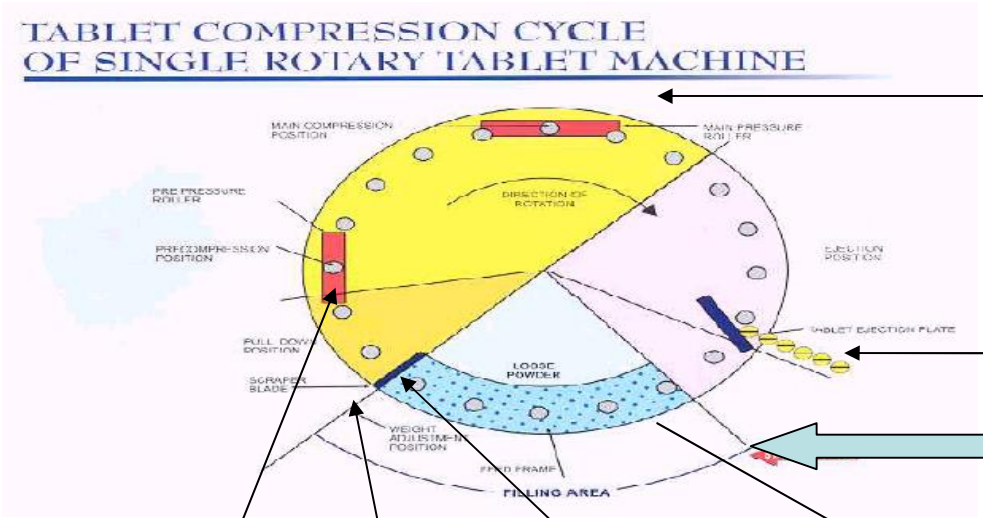


- The tablet press is a high-speed mechanical device. It 'squeezes' the ingredients into the required tablet shape with extreme precision.
- It can make the tablet in many shapes, although they are usually round, capsule or oval.
- Also, it can ‘Engrave’ the name of the manufacturer or the product on the surface of the tablet as Monogram/Break-line.
- Each tablet is made by pressing the granules inside a die cavity made of hardened steel.
- The die is a disc shape with a hole cut through its center.
- The powder is compressed under high pressure in the center of the die by upper and lower steel punches that fit into the top and bottom of the die.

SR. NO.	QUESTION ANSWER

Compression Machine Cycle





Main Pressure Pressure Roller

Tablet Ejection Plate

Start of cycle

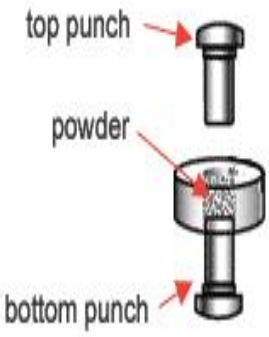
Pre compression

Weight adjustment

Scrapper blade

Feed frame

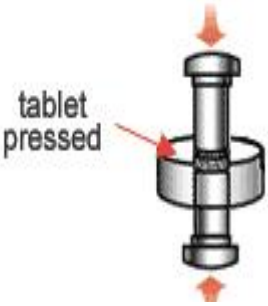
SR. NO.	QUESTION ANSWER



•Stage I: Top punch is withdrawn from the die by the upper cam
Bottom punch is low in the die Powder falls in through the hole and fills the die.



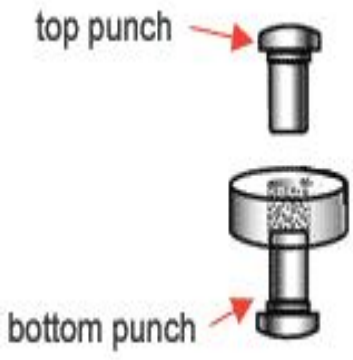
•Stage II: Bottom punch moves up to adjust the powder weight it



•Stage III: Top punch is driven into the die by the upper cam.
Bottom punch is raised by the lower cam.
Both punch heads pass between heavy rollers to compress the powder



Stage IV: Top punch is withdrawn by the upper cam
Lower punch is pushed up and expels the tablet
Tablet is removed from the die surface by the surface plate



•Stage V: Back to Original Stage.

SR. NO.	QUESTION ANSWER

Problems in Tabletting

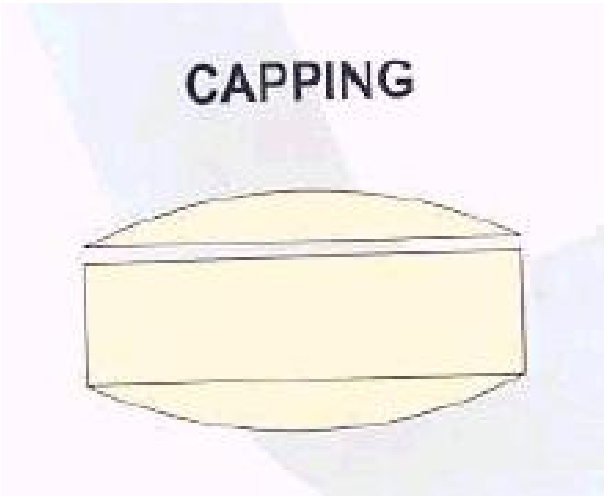
1. Capping

Causes for Capping			Solutions
Tooling	Machine	Granules	
• Die bores having rings. • Too much depth of concavity in punches.	• Excessive Pressure • Compression taking place at lower side of die. • Too much of vibration.	• Excessive lubrication. • Too dry granules. • Less binder in granules / More fines.	• Replace dies if found defective/Polishing/ Change the upper punch penetration. • Reduce compression pressure. • Improve granulation. • Check 'LOD' of the Granules

2. Sticking/Picking

(Refer Fig 3 and 4 on slide no. 56)





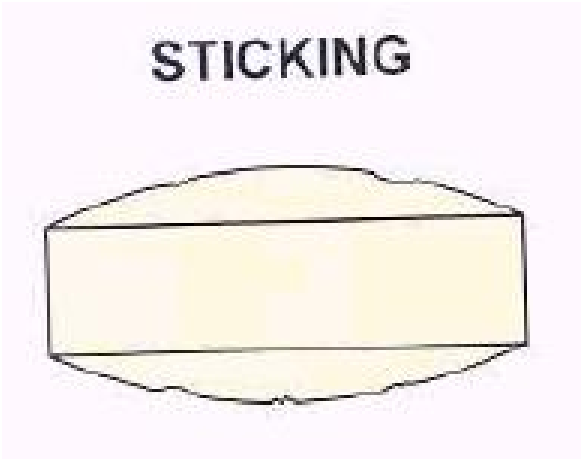
SR. NO.	QUESTION ANSWER

2. Sticking/Picking

Causes for Sticking/ Picking			Solutions
Tooling	Machine	Granules	
• Wrong design of embossing or break line. • Punch face having pitting marks	• Less compression pressure. • Too much heat generation due to wrong setting of feed frames/gears/ turret etc.	• Excessive moisture. • Insufficient lubrication	• Change embossing design. • Increase pressure. • Improve granulatio • Check the 'LOD' o the Granules.

Note : Check the Relative – Humidity of the area for Humidity sensitive products





3.Black marks on Tablets

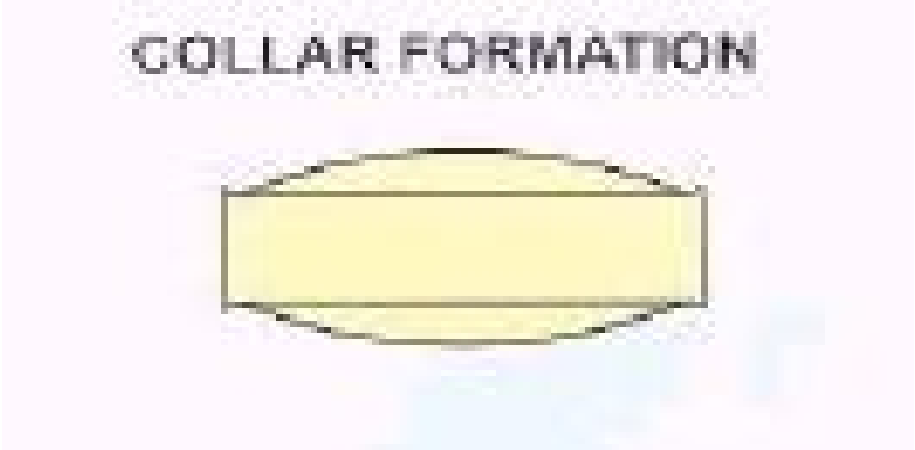
Causes for Black Marks on Tablets			Solutions
Tooling	Machine	Granules	
• Tight upper punch may be scrapping the Cam Track and Punch Guide.	• Turret running tight with cam track • Improper feed frame setting. • Lubrication gears or oil may be contaminating the powder.	• Excessive moisture. • Over sized granules. • Granules having black particles prior to compression.	• Use of dust cups on upp punches. • Rectify machine problen • Set feed frame properly. • Reduce lubrication for upper punches. • Improve granules quality

SR. NO.	QUESTION ANSWER



4.Collar formation

Causes -Collar Formation on Tablets			Solutions
Tooling	Machine	Granules	
• Worn out punches and dies. • Wrong polishing methods result in blunt tip corners.	• Nil	• Too much of fines.	• Replace defective tool • Provide Training to polishing operators. • Improve granules.



SR. NO.	QUESTION ANSWER

5.Non- Uniform Weight

Causes -Collar Formation on Tablets			Solutions
Tooling	Machine	Granules	
• Non- uniform lower punch working length. • Die height is above the standard limit. • Lower punch Jamming.	• Defective feed frame or improper setting. • High M/C speed. • Excessive vibrations. • Worn-out weight Dozzer. • In-correct 'cams'	• Non-uniform, too big, too fine granules. • Granules sticking to the lower punches.	• Replace/ rectify too found defective. • Clean the lower pu • Reduce machine sp replace worn-out p and feed frame. • Reduce the pressur • Provide uniform Granules.

6.Non- Uniform Tablet Thickness

Causes- Non-uniform Tablet Thickness			Solutions
Tooling	Machine	Granules	
• Non-uniform lower punch working length. • Worn-out Head.	• Worn out pressure rollers. • Excessive vibrations. • High M/C speed.	• Non-uniform, too big, too fine granules. • Granules sticking to the lower punches	• Replace/ rectify tools, found defective. • Reduce machine spee replace worn-out parts and feed frame. • Provide uniform Granules.

SR. NO.	QUESTION ANSWER

TABLET COATING

Why Coating is required ?

The application of coating to Tablets, which is an additional step in the manufacturing process, increases the cost of the product; therefore, the decision to coat a tablet is usually based on one or more of the following objectives

1. To mask the taste, odour, and appearance of the drug.
2. To provide physical and chemical protection for the drug from atmospheric effects, temperature, humidity and light.
3. Functional coating (Control release, enteric coat, sugar syrup coat).
4. To protect the drug from the gastric environment of the stomach with an acid-resistant enteric coating.
5. To incorporate another drug or formula adjuvant in the coating to avoid chemical incompatibilities or to provide sequential drug release
6. To improve the Pharmaceutical elegance by use of special colours and contrasting printing, which improves the appearance of the product.

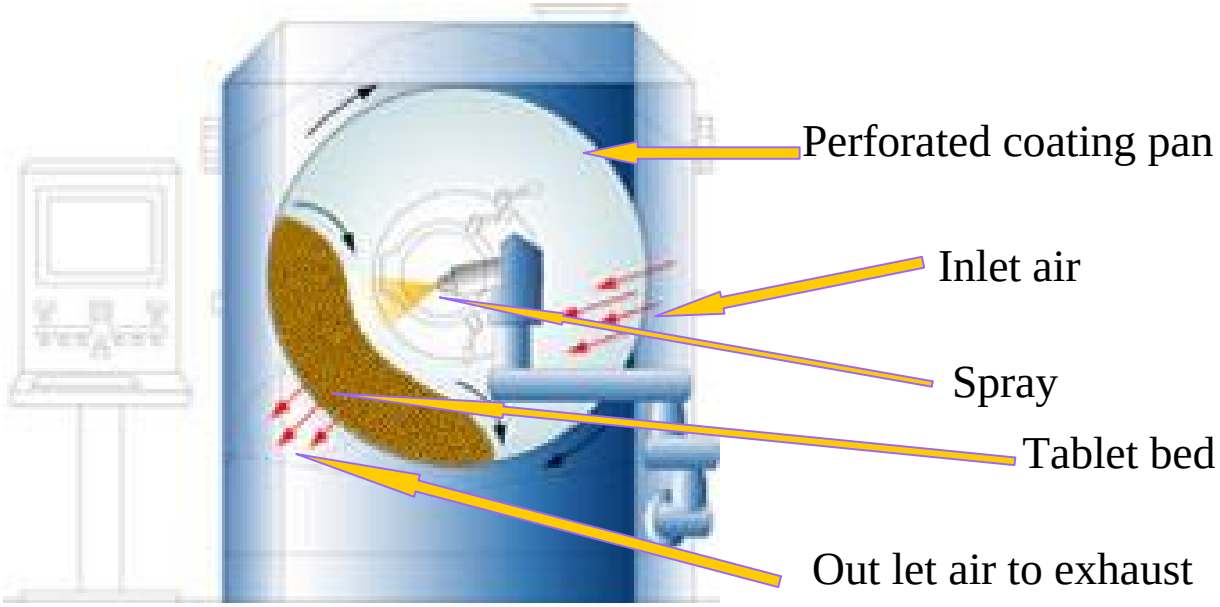
Conventional Pan coaters

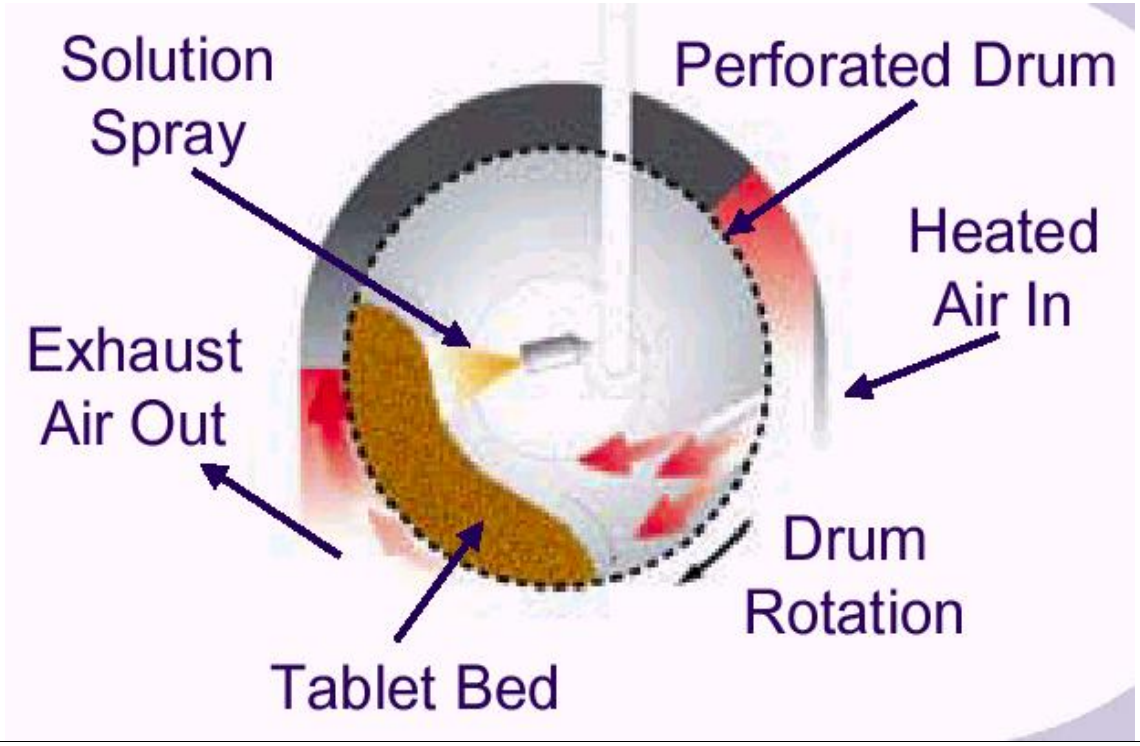


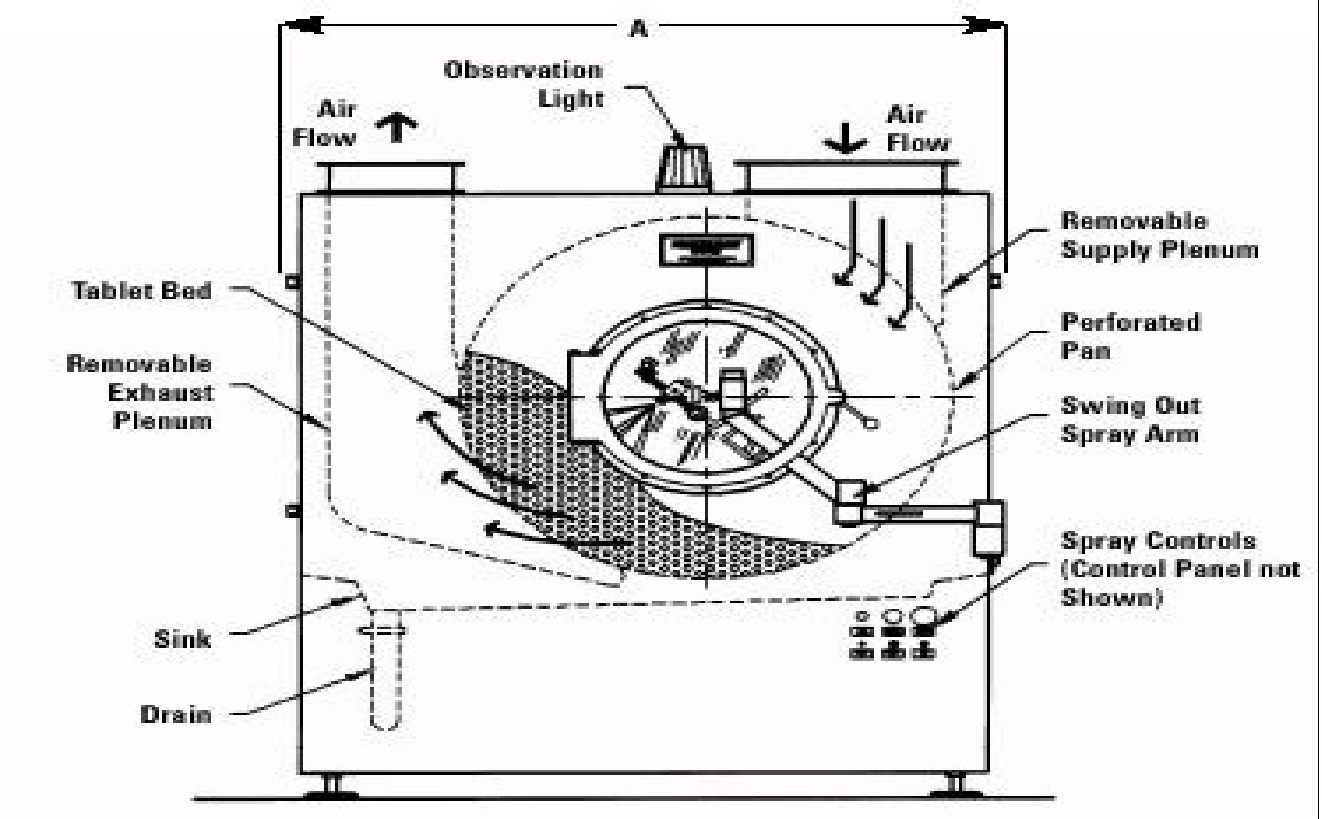
- The pan coaters are most commonly used for the film coating application.

SR. NO.	QUESTION ANSWER

Modern Coating Pan

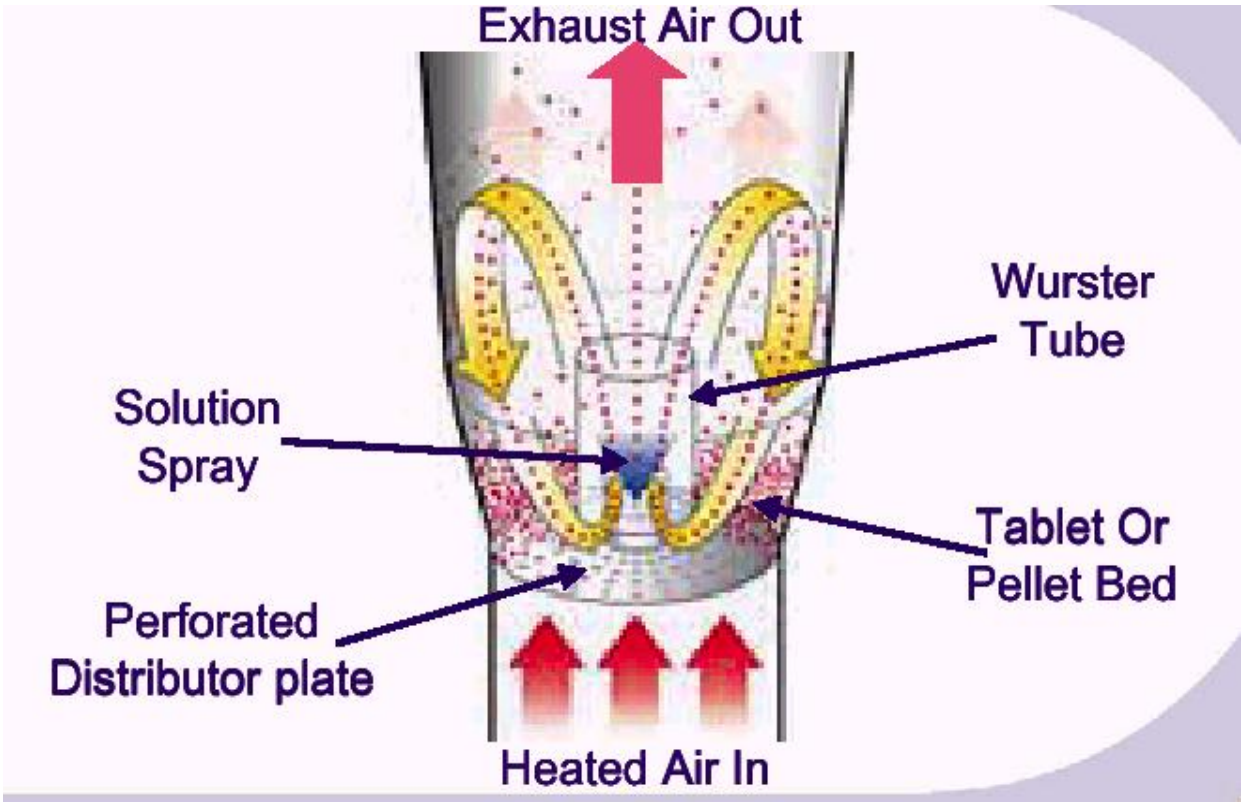




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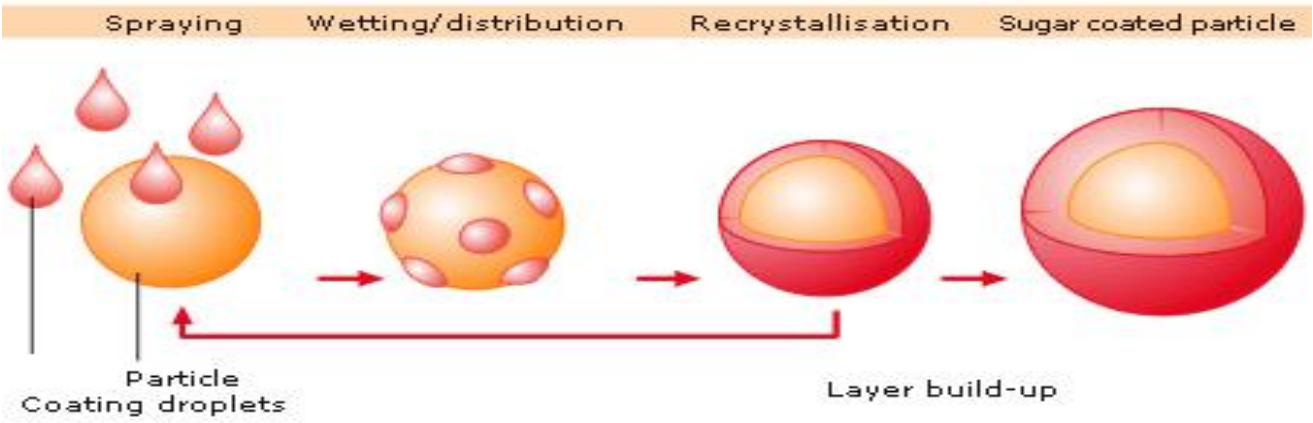
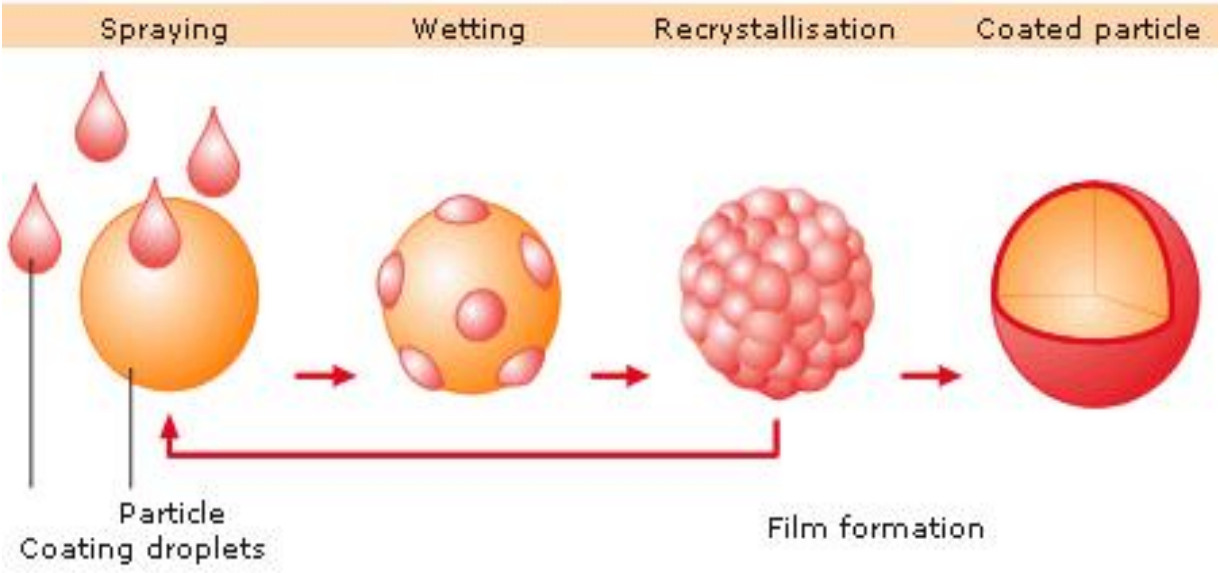
Fluidized Bed Wurster Coating process



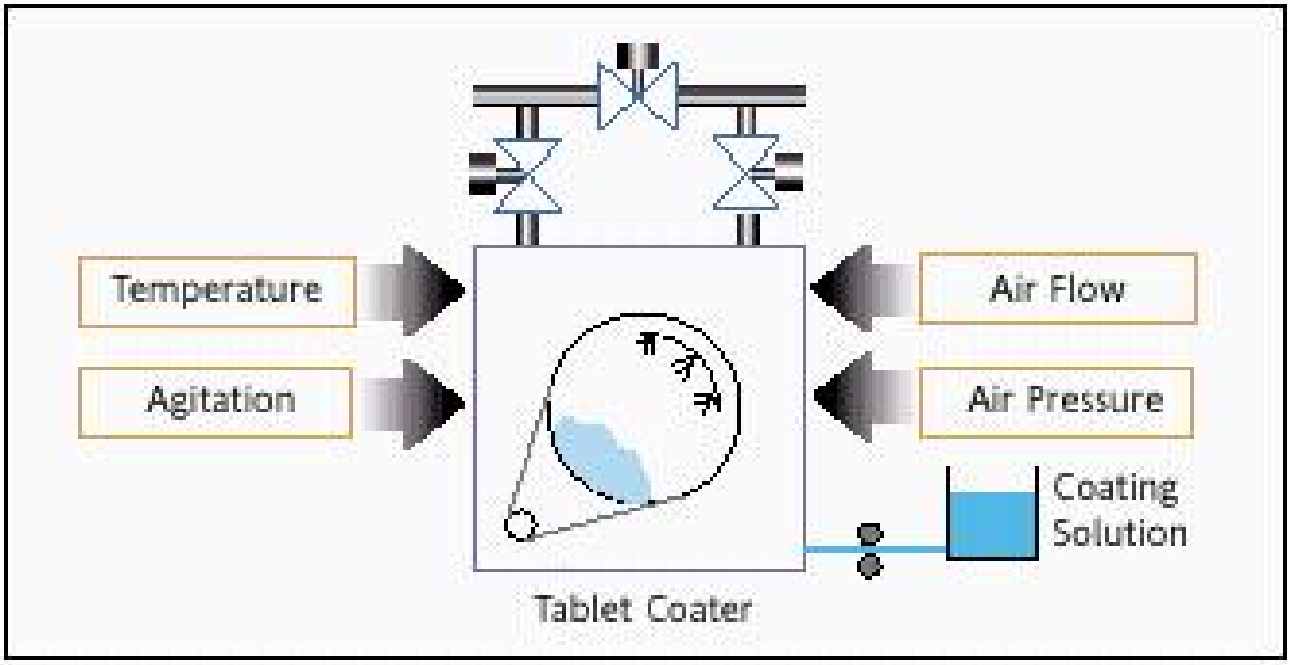
Types of Coating

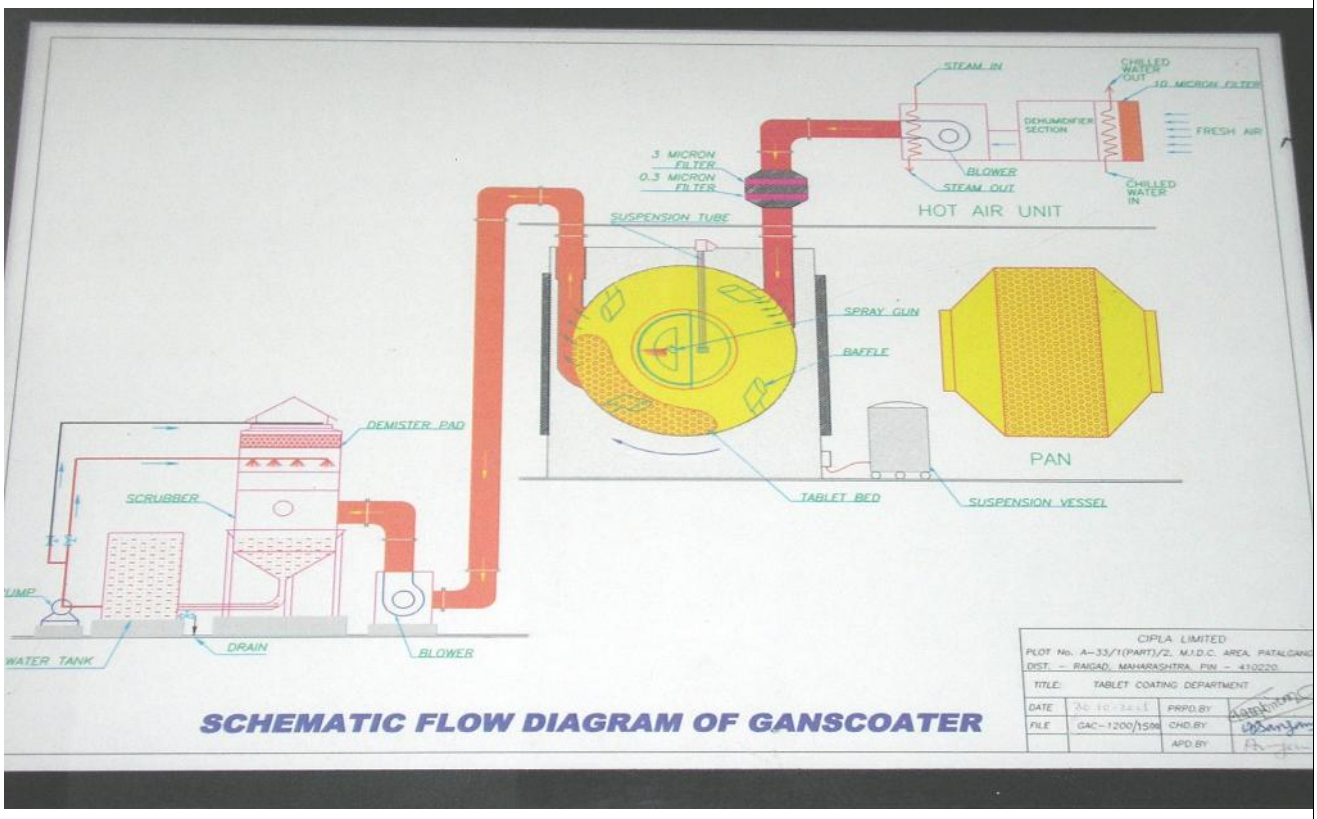
- Sugar Coating
- Film Coating
- Compression Coating
- Sugar coating gives excellent appearance to the tablets.
- Sugar Coating process involves following steps:

1. Sealing.
2. Sub coating.
3. Syruping.
4. Finishing
5. Polishing

SR. NO.	QUESTION ANSWER
	Sugar Coating Process  **Film Coating Process** 

SR. NO.	QUESTION ANSWER





SR. NO.	QUESTION ANSWER



Possible Causes:

- Too little coating applied
- Inadequate mixing of tablets during coating

Poor opacity (or hiding power) of coating

- Solids content of coating liquid is too high
- Insufficient number of spray guns

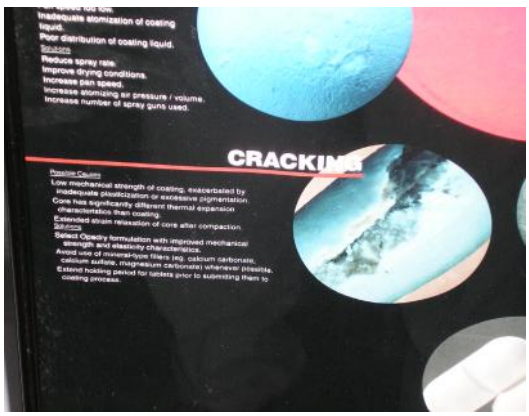


Cracking



Possible Causes:

- Low mechanical strength of coating, exacerbated by inadequate plasticization or excessive pigmentation
- Core has significantly different thermal expansion characteristics than coating
- Extended elastic recovery of core after compaction
- Inadequate plasticization



SR. NO.	QUESTION ANSWER

Twinning



Possible Causes:

- Spray rate too high
- Pan speed too low
- Inappropriate tablet shape
- Tacky coating formulation.

Peeling

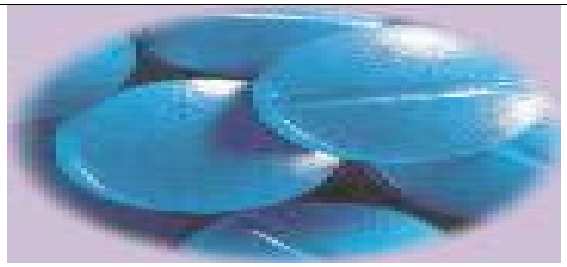


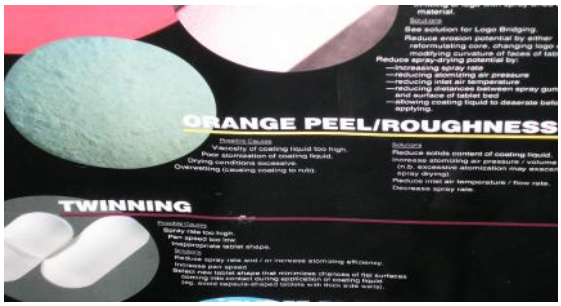


Possible Causes:

- Low mechanical strength of coating.
- Poor adhesion of coating to tablet surface.
- Excess lubricant usage in formulation.

SR. NO.	QUESTION ANSWER





Possible Causes:

- Viscosity of coating liquid too high
- Poor atomization of coating liquid

Logo Bridging





Possible Causes:

- Inadequate adhesion of the film coating
- Surface characteristics of the product being coated(e.g. hydrophobic substrate)
- Inappropriate design of logo(e.g. too detailed or too fine)
- Insufficient plasticizer in film / high internal stress

SR. NO.	QUESTION ANSWER

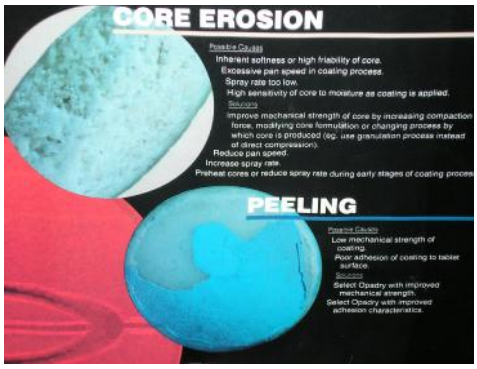




Possible Causes:

- Spray rate too high
- Inadequate drying conditions
- Pan speed too low
- Inadequate atomization of coating liquid
- Poor distribution of coating liquid





Possible Causes:

- Inherent softness or high friability of core.
- Excessive pan speed in coating process.
- Spray rate too low.
- Low solids content of spray solution.
- Premature swelling of hydrophilic super disintegrant in formulation

SR. NO.	QUESTION ANSWER





Possible Causes:

- Low mechanical strength of coating.
- Excessive pan speed.
- Low solids content in coating liquid.
- Low spray rate.
- Sharp edges on tablets.
- Worn tablet punches.
- Low tablet hardness / friability



Possible Causes:

- Inappropriate design of logo (e.g. too detailed or too fine.
- Logo "disappearance" can be due to erosion of tablet surface around logo.
- Logo Bridging.
- In-filling of logo with spray-dried coating material.

SR. NO.	QUESTION ANSWER
50.0	**BALANCE CALIBRATION**
50.1	❖ Balance Calibration is one of the most important aspects in Pharmaceutical industry. ❖ The effect of a drug can vary considerably even with very small variations in dosage quantities. ❖ It is therefore very essential to have a high degree of accuracy in all operations involving quantisation of dosage forms. ❖ **FOR ANALYTICAL BALANCE:** **(I) General Calibration:** ❖ Place standard weight as specified one by one on the pan and note down the observations in the balance calibration record. ❖ Draw the linearity curve for the above readings and find out the correlation factor. ❖ **Acceptance Criteria:** The observed weight should not deviate by ± 0.1% of actual weight or ± 2 x least count which ever is more of the certified weight and the Correlation factor should not be less than 0.9999. ❖ **FREQUENCY: Quarterly** ï 7 days **(II) Ascentric Calibration:** ❖ Place standard weight as specified in four corners and center of the pan one by one and note down the readings in balance calibration record. ❖ Calculate % RSD. ❖ **Acceptance Criteria:** % RSD- NMT 0.1 % ❖ **FREQUENCY: Quarterly** ï 7 days ❖ **FOR PLATFORM BALANCE:** **(I) Accuracy:** ❖ Check the accuracy of the balance by using 5 standard weights. ❖ Place standard weight one by one in the center of the platform and record the observations in the balance calibration record. ❖ **Acceptance Criteria:** The observed weight should not deviate by ± 0.1% of actual weight or ± 2 x least count which ever is more of the certified weight. ❖ Frequency: Quarterly ± 7 days **(II) Corner Load test:** ❖ Place standard weight in four corners and center of the balance one by one and note down the readings in respective balance calibration record. ❖ Calculate % RSD. ❖ Record the observations in the balance calibration record. ❖ **Acceptance Criteria:** The observed weight should not deviate by ± 0.1% of actual weight or ± 2 x least count which ever is more of the certified weight. ❖ **%** RSD : NMT 0.5 **%** ❖ Frequency: Quarterly ± 7 days

SR. NO.	QUESTION ANSWER
51.0	**IPQA**
51.1	As per British Pharmacopoeia:

Pharmaceutical Dosage forms	Average Weight	% Deviation
Tablets (Uncoated and Film Coated)	80 mg or less	10 %
	More than 80 mg and les than 250 mg	7.5 %
	250 mg or more	5 %
Capsules, Granules (Uncoated single dose) and Powder (Single dose)	Less than 300 mg	10 %
	300 mg or more	7.5 %

As per United States Pharmacopoeia;

Pharmaceutical Dosage forms	Average Weight	% Deviation
Tablets (Uncoated and Film Coated)	130 mg or less	10 %
	More than 130 mg and les than 324 mg	7.5 %
	324 mg or more	5 %
Capsules, Granules (Uncoated single dose) and Powder (Single dose)	Less than 300 mg	10 %
	300 mg or more	7.5 %

Friability

For tablets with a unit mass equal to or less than 650 mg, take a sample of whole tablets corresponding as near as to 6.5 gm.

For tablets with a unit mass of more than 650 mg, take a sample of 10 whole tablets.

Friability test is done to withstand the mechanical shocks during manufacturing, packing and shipping.

Friability % = $\frac{I - F}{} \times 100$

SR. NO.	QUESTION ANSWER

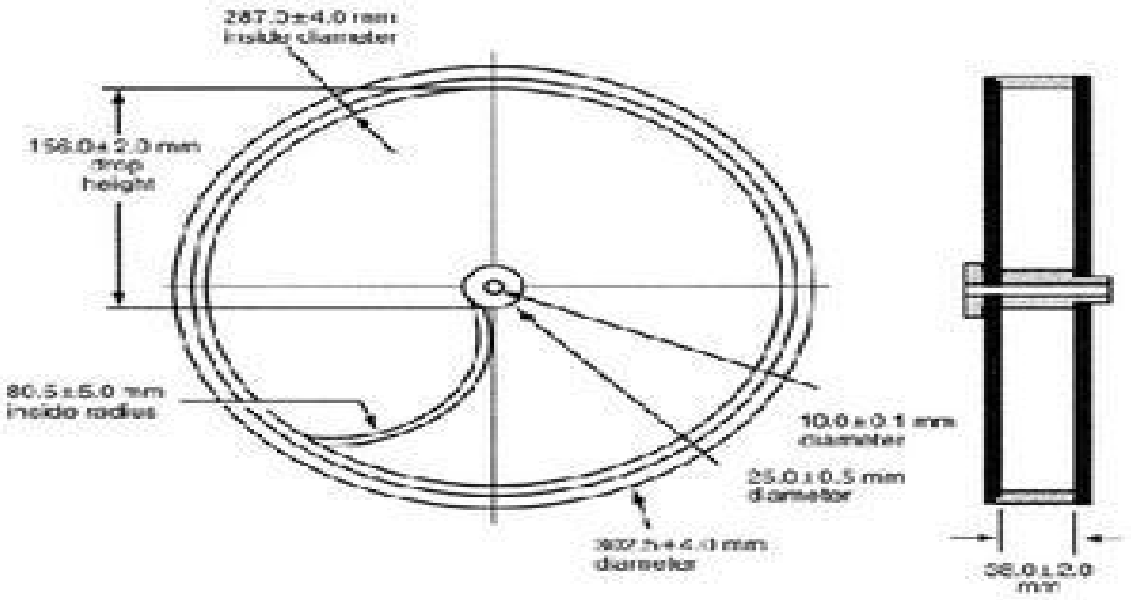
$$\frac{I}{I : \text{Initial weight of tablet}}$$
F: After friability weight

Tablet friability Apparatus:
Friability test apparatus is common for official pharmacopeias in BP, USP.

- Friability test apparatus consists of:
  A drum with an internal diameter between 289-291mm and a depth between 36-40 mm, of transparent synthetic polymer with polished internal surface.

  One side of the drum is removable.
  The tablets are tumbled at each turn of the drum by a curved projection with inside radius between 75.5-85.5 mm that extends from the middle of the drum to the outer wall.

  The outer diameter of the central ring is between 24.5-25.5 mm.
  The drum is attached to the horizontal axis of the device that rotates at 25 ± 1 r/min.



If tablet size or shape causes irregular tumbling, adjust the drum base so that the base forms an angle of about 10 with the horizontal and the tablets no longer bind together when lying next to each other, which prevents them from falling freely.

DISINTEGRATION TEST

Disintegration test is done to determine whether tablets or capsules disintegrate **within prescribed time** when placed in a liquid medium under the experimental conditions.

SR. NO.	QUESTION ANSWER

Complete disintegration is defined as that state in which any **residue of the unit, except fragments** of insoluble coating or capsule shell remaining on the screen of the test apparatus or adhering to the lower surface of the discs, if used, is a soft mass having no palpably firm core.

Disintegration apparatus

The apparatus is common for official pharmacopieas of IP,BP,USP.

The disintegration apparatus consists of :

- The basket-rack assembly

It consists of 6 open ended transparent tubes each 77.5 ± 2.5 mm long and having inside diameter of 21.85 ± 1.15 mm and a wall 1.9 ± 0.9 mm thick

The tubes are held in a vertical position by 2 plates, each 90 ± 2 mm in diameter and 6.75 ± 1.75 mm in thickness with 6 holes, each 24 ± 2 mm in diameter, equidistant from the center of the plate and equally spaced from one another.

Attached to the under surface of the lower plate is a woven stainless wire cloth with 2.0 ± 0.2 mm mesh appertures.

1 liter beaker, 149 ± 11 mm in height and inside diameter of 106 ± 9 mm for the immersion fluid. A thermostatic arrangement for heating the fluid between 35 °C and 39 °C.

A device for raising and lowering the basket in the immersion fluid at a constant frequency rate between 29 and 32 cycles per minute, through distance of 55 ± 2 mm.

The volume of the fluid in the vessel is such that at the highest point of the upward stroke the wire mesh remains at least 15 mm below the surface of the fluid, and descends to not less than 25 mm from the bottom of the vessel on the downward stroke. At no time should the top of the basket rack assembly become submerged.

The time required for the upward stroke is equal to the time required for downward stroke, the change in the stroke direction is a smooth transition rather than abrupt reversal of motion

- Discs:

The use of disc is permitted only where specified or allowed.

Each tube is provided with a cylindrical disc with diameter of

20.7 ± 0.15 mm with thickness of 9.5 ± 0.15 mm.

5 parallel holes extend between the ends of the cylinder with a diameter of 2 ± 0.1 mm.

SR. NO.	QUESTION ANSWER

Procedure:
Place 1 dosage unit in each of the 6 tubes of the basket and if prescribed add a disc.
Operate the apparatus using specified medium maintained at 37 ± 2 ºC as the immersion fluid.
At the end of the specified time lift the basket from the fluid and observe the dosage units.

- Acceptance criteria:
  All of the dosage units should have completely disintegrated.

If 1 or 2 dosage units fail to disintegrate, repeat the test on 12 additional dosage units.
The test passes if not less than 16 of the 18 dosage units tested have disintegrated.

Sr. no.	Type of tablet	Limit
1.	Uncoated tablets	Not more than 15 min
2.	Coated tablets	Not more than 60 min
3.	Effervescent tablets	Not more than 05 min
4.	Soluble tablets	Not more than 03 min
5	Dispersible tablets	Not more than 03 min
6.	Orodispersible tablets	Not more than 03 min
7.	Enteric coated tablets	In 0.1 M HCL for 2 hrs – No crac In phosphate buffer solution pH 6 NMT 60 min

DISSOLUTION

Types of dissolution test apparatus:

- Basket apparatus
- Paddle apparatus
- Reciprocating cylinder apparatus
- Flow- through cell

The requirements are met if the quantities of active substance dissolved from the dosage units tested conform to acceptance table. Continue testing through the 3 levels unless the results conform at either S_1 or S_2. The quantity Q, is the specified amount of dissolved active substance, expressed as a percentage of the labeled content; the 5 per cent, 15 per cent, and 25 per cent values in the acceptance table are percentages of the labeled content so that these values and Q are in the same terms.

SR. NO.	QUESTION ANSWER

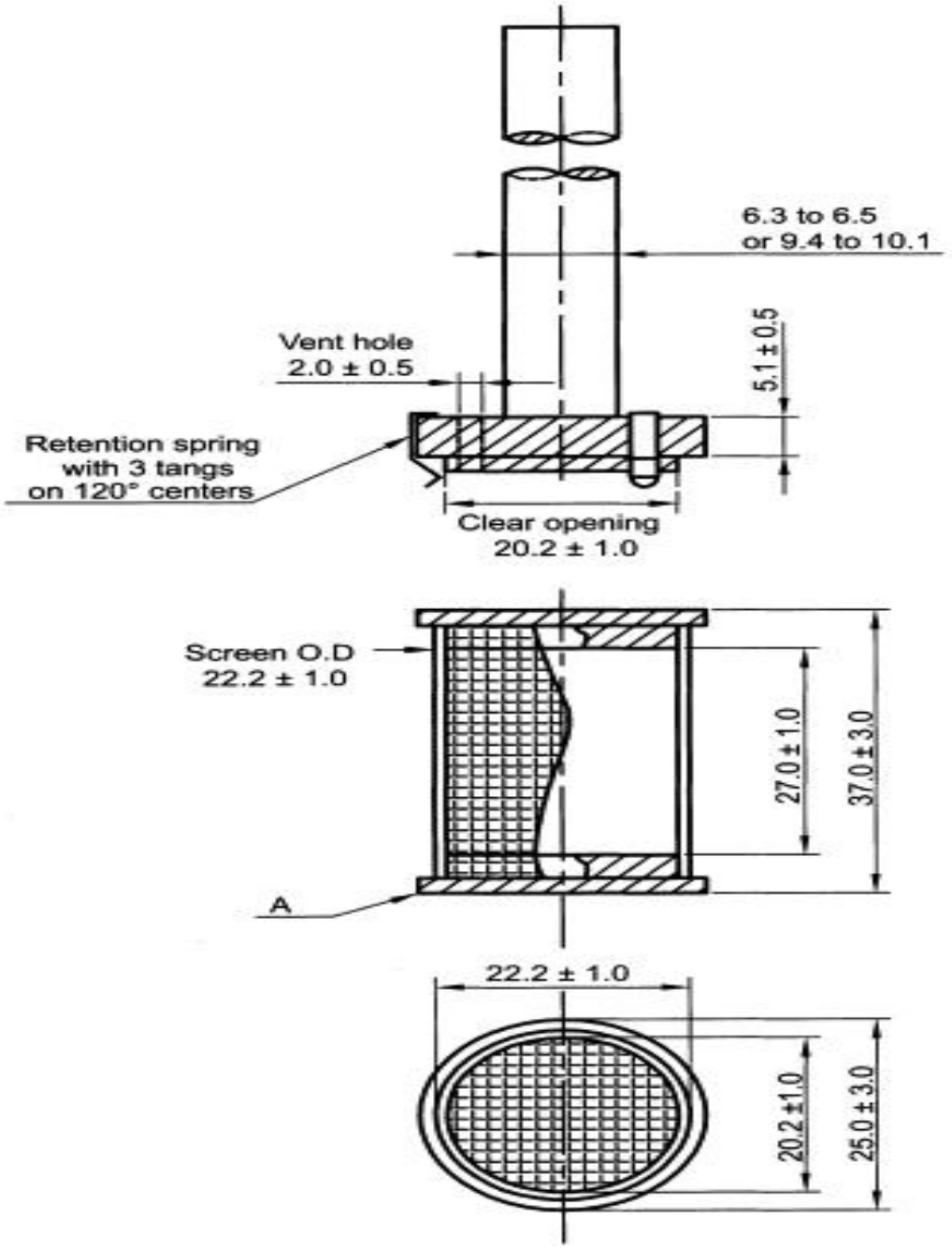
Immediate release dosage forms

Level	Number tested	Acceptance Criteria
S_1	6	Each unit is not less than Q + 5 percent
S_2	6	Average of 12 units (S_1 + S_2) is equal to or greater than Q-15 percent
S_3	12	Average of 24 units (S_1 + S_1 + S_1) is equal to or greater than Q , not more than 2 units are less than Q-15 percent and no is less than Q-25 percent.

Immediate release dosage forms Pooled sample

Level	Number tested	Acceptance Criteria
S_1	6	Average amount dissovled is not less than Q + 10 percent
S_2	6	Average amount dissolved (S_1 + S_2) is equal to or greater than Q + 5 percent
S_3	12	Average amount dissolved (S_1 + S_1 + S_1) is equal to or greater than Q .

SR. NO.	QUESTION ANSWER

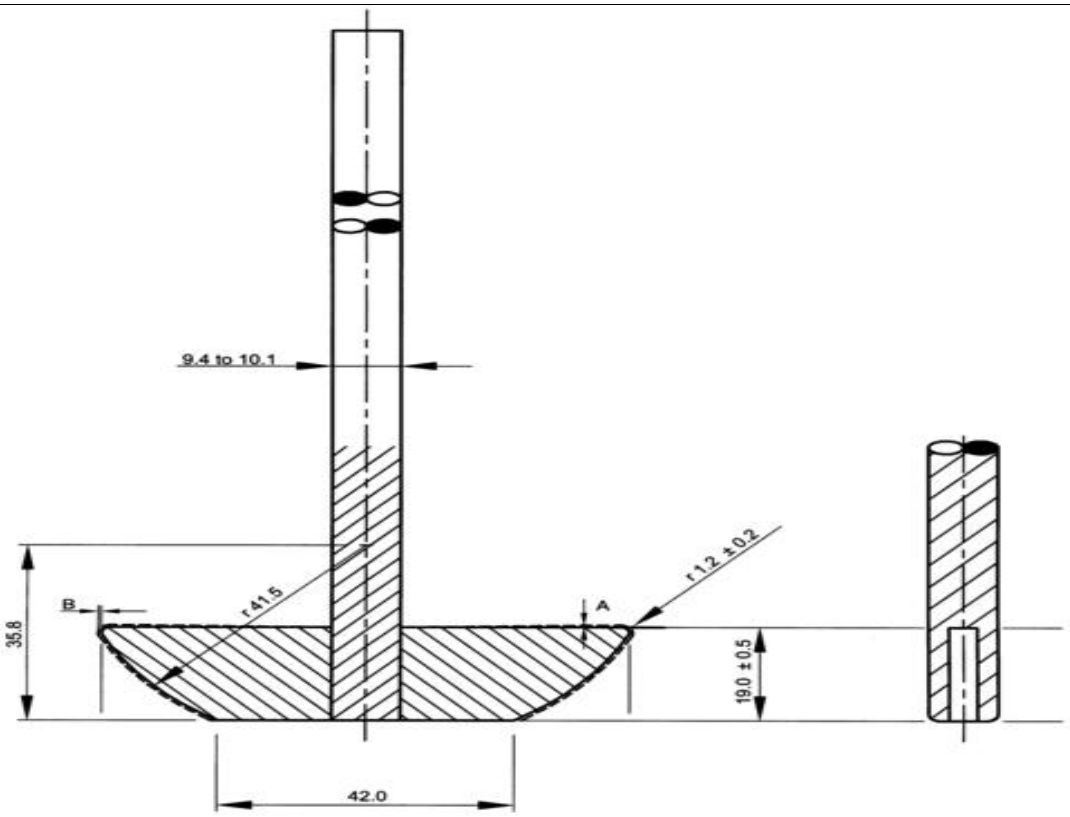


1) Screen with welded seam: 0.25-0.31 mm wire diameter with wire opening of 0.36-0.44 mm. After welding the screen may be slighty altered.

2) Maximum allowable runout at "A" is 1.0 mm when the part is rotated on center line axis with basket mounted.

Figure 2.9.3.-1. — *Apparatus 1, Basket stirring element*
Dimensions in millimetres

SR. NO.	QUESTION ANSWER



A and B dimensions do not vary more than 0.5 mm when part is rotated on center line axis.
Tolerances are ± 1.0 mm unless otherwise stated.

Figure 2.9.3.-2. — *Apparatus 2, Paddle stirring element*
Dimensions in millimetres

Uniformity of Dosage Units

- The term “uniformity of dosage unit” is defined as the degree of uniformity in the amount of the drug substance among dosage units.
- The uniformity of dosage units can be demonstrated by either of two methods,
- *Content Uniformity* or *Weight Variation*

- The test for Content Uniformity is based on the assay of the individual content of drug substance's in a number of individual dosage units to determine whether the individual content is within the limits set.

SR. NO.	QUESTION ANSWER

Dosage Form	Type	Subtype	Dose & Ratio ofDrug Substance	
			25 mg & 25%	<25 mg or <25%
Tablets	Uncoated Coated	Film Others	WV	CU
Capsules	Hard Soft	Suspensionsemulsions, gels	WV	CU

TYPES OF TABLET:-

IP	BP	USP
Uncoated	Uncoated	Compressed/molded
Film Coated	Coated	Plain Coated
Enteric Coated	Gastro Resistant (Enteric Coated)	Delayed Release
Dispersible Tablet	Dispersible Tablet	Dispersible Tablet
Modified Release Tablet	Modified Release Tablet	Extended Release Tablet
Soluble Tablet	Soluble Tablet	Soluble Tablet
Effervescent Tablet	Effervescent Tablet	Effervescent Tablet
For use in mouth (Chewable, Lozenges, Sublingual)	For use in mouth (Chewable, Lozenges, Sublingual)	Chewable/Buccal, Sublingua
Orodispersible	Orodispersible	Orodispersible

SR. NO.	QUESTION ANSWER

STANDARDS FOR TABLETS:-

IP	BP	USP
Content of Active Ingredient (API)	Content of Active Ingredient (API)	Content of Active Ingredient
Uniformity of weight	Uniformity of weight	Weight Variation
Uniformity of Content	Uniformity of Content	Uniformity of Content
DT	DT	DT
Dissolution	Dissolution	Dissolution

1) CONTENT OF ACTIVE INGREDIENT: -

1) Assay of Active
2) 20 tabs: - Limits 90% to 110%

2) UNIFORMITY OF WEIGHT/WT VARIATION:-

20 tabs, calculate avg. wt NMT 2 deviate, none twice the limits.

51.2

Weight Variation Limits:-

1) For Tablets

IP/BP	Limit	USP
80 mg or less	10%	130mg or less
More than 80mg or Less than 250mg	7.5%	130mg to 324mg
250mg or more	5%	More than 324mg

2) For Capsule:-

IP	Limit
Less than 300mg	10%
300mg or More	7.5%

SR. NO.	QUESTION ANSWER
	3) FRIABILITY TEST:- This test is additional to check crushing strength of tablet by this test one can check Capping &/ Lamination. USP limit is 0.5 to 1%. Rotation: - 25 rpm or 100 rotations in 4 min. **4) USP 36 - 905 UNIFORMITY OF DOSAGE:-** **UNIFORMITY OF CONTENT OR CONTENT UNIFORMITY:-** **IP: -** Active less than 10mg or 10%, **BP: -** Active less than 2 mg or 2%, **USP: -** Active less than 25mg or 25%. -10 tabs limit NMT 1 tab deviate 85 – 115% & none outside 75 – 125% of the Avg value/IP/BP/USP (Relative Standard Deviation less than or equal to 6%), - If 2 or 3 individual values are outside the limits 85 – 115% of the Avg value, & none outside 75 – 125% repeat for 20 tabs. - Complies when 30 tabs NMT 3 of the individual values are outside the limit 85 – 115% of the Avg value, and none outside 75 – 125%. **5) DISINTEGRATION TIME:-**
	Uncoated Tablet — NMT 15 min, in water with Disc $37^0C \pm 2^0C$ **Coated Tablet** — NMT 30 min, In water with Disc for **Film Coated Tab**, and NMT 60 min Other than Film coated tablet **Enteric Coated Tab** — Intact for 1 hr in 0.1 N HCl & disintegrate within 2 hr in Mixed 6.8 Phosphate buffer. According to USP 1 hr in Simulated gastric fluid, then in Simulated Intestinal Fluid. **Dispersible/Soluble** — Within 3 min in water at $25^0C \pm 1^0C$ (**IP**) & 15 – 25^0C (**BP**) **Orodispersible** — Within 1 min **Effervescent Tab** — 5 min in 250 ml water at 20 – 30^0C (**IP**) & 5 min in 200 ml water at 15-25^0C (**BP**) **Buccal & Sublingual** — Not Applicable but dissolve within 15 – 30 min.
51.3	**DT Apparatus:-** Mesh Apperture:- 2mm (#10), Cycles:- 28 – 32 cycles/min, 50 – 60 mm distance from bottom & top, Temp of water $37^0C \pm 2^0C$. ***If 1 or 2 tabs fail, repeat for 12 tabs.***

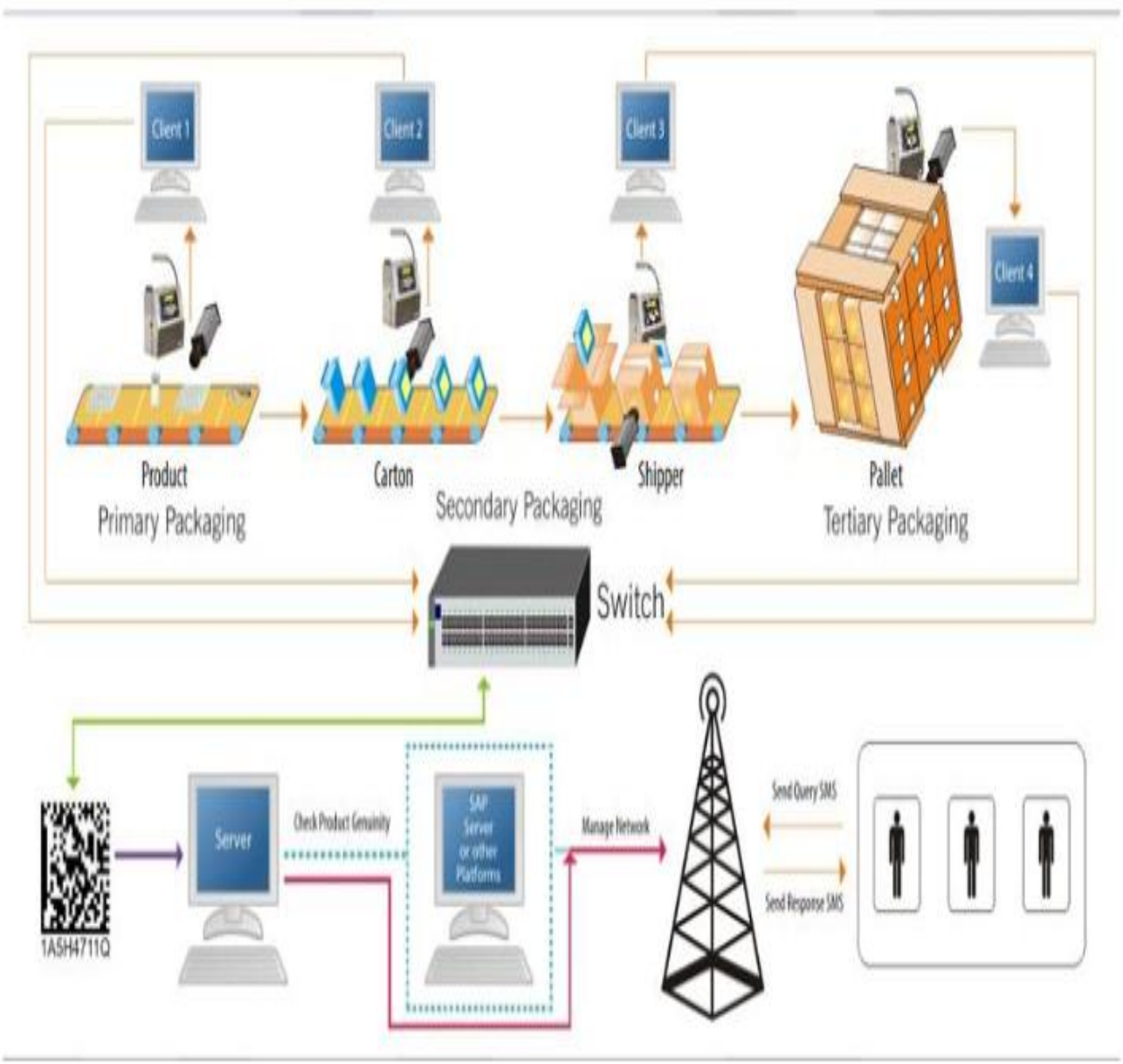
SR. NO.	QUESTION ANSWER

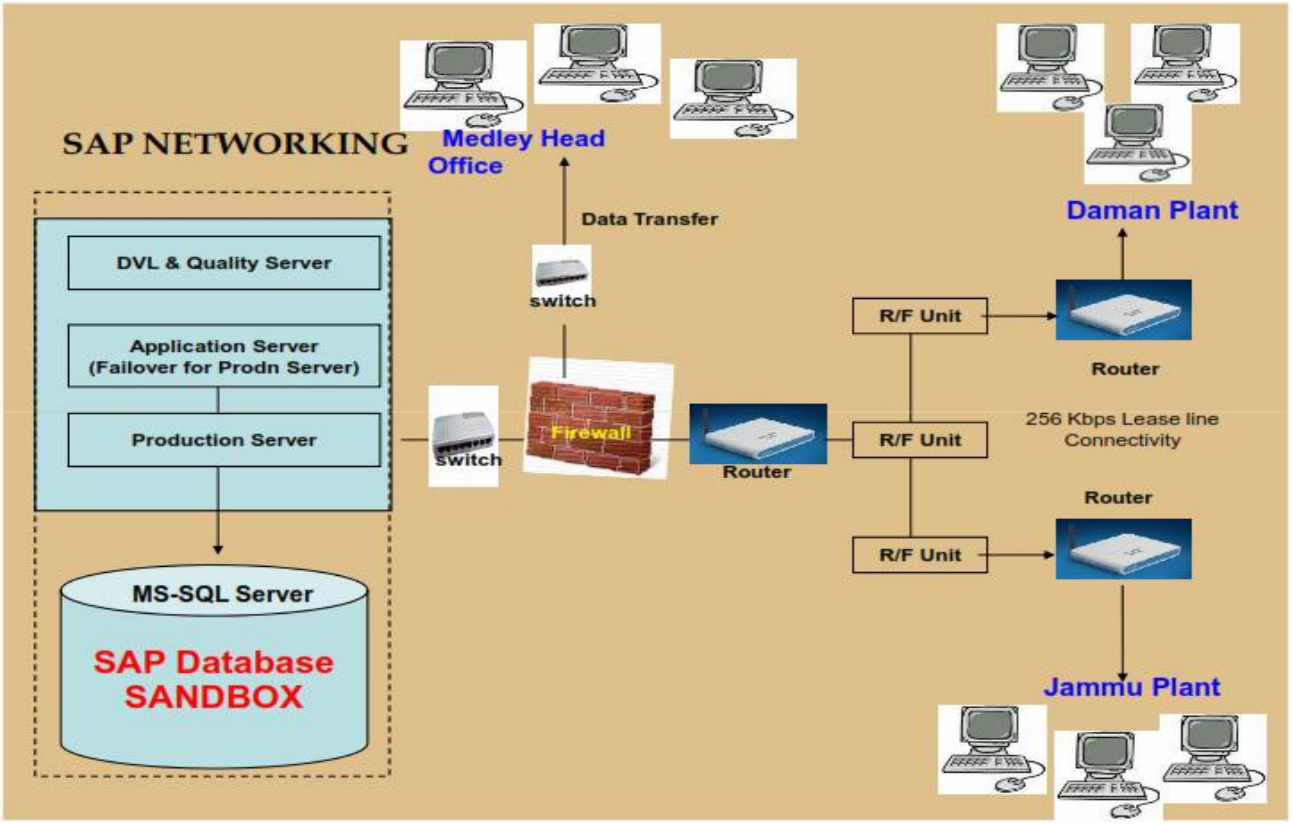
51.4

LIST OF PHARMACOPEIAS

Sr. No.	Name of Pharmacopeia	Version	Volume	Effective Date	Addendum		Supplement		Remarks
01	IP	2014	I,II,III,IV	1st Jan 2014	NA		NA		NA
02	BP	2014	I,II,III,IV,V	1st jan 2014	Addendum-1 (Veternary)	1st Jan 2014	NA		Under purchase (BP 2013 available)
03	USP	USP36 NF 31	I,II,III	1st May 2013	Addendum - 1 (2014)		Supplement - I	1st Aug 2013	NA
							Supplement - II	1st Dec 2013	NA
04	Ph.Eu.	7th Edition	7.0 (Volume -I)	01/2011	Addendum- 1 (2014)		7.1	04/2011	NA
							7.2	07/2011	
							7.3	01/2012	
							7.4	04/2012	
			7.0 (Volume - II)	01/2011			7.5	07/2012	
							7.6	01/2013	
							7.7	04/2013	
							7.8	07/2013	

PHARMA BOOK

SR. NO.	QUESTION ANSWER
52.0	**ONLINE SYSTEM FLOW**
52.1	

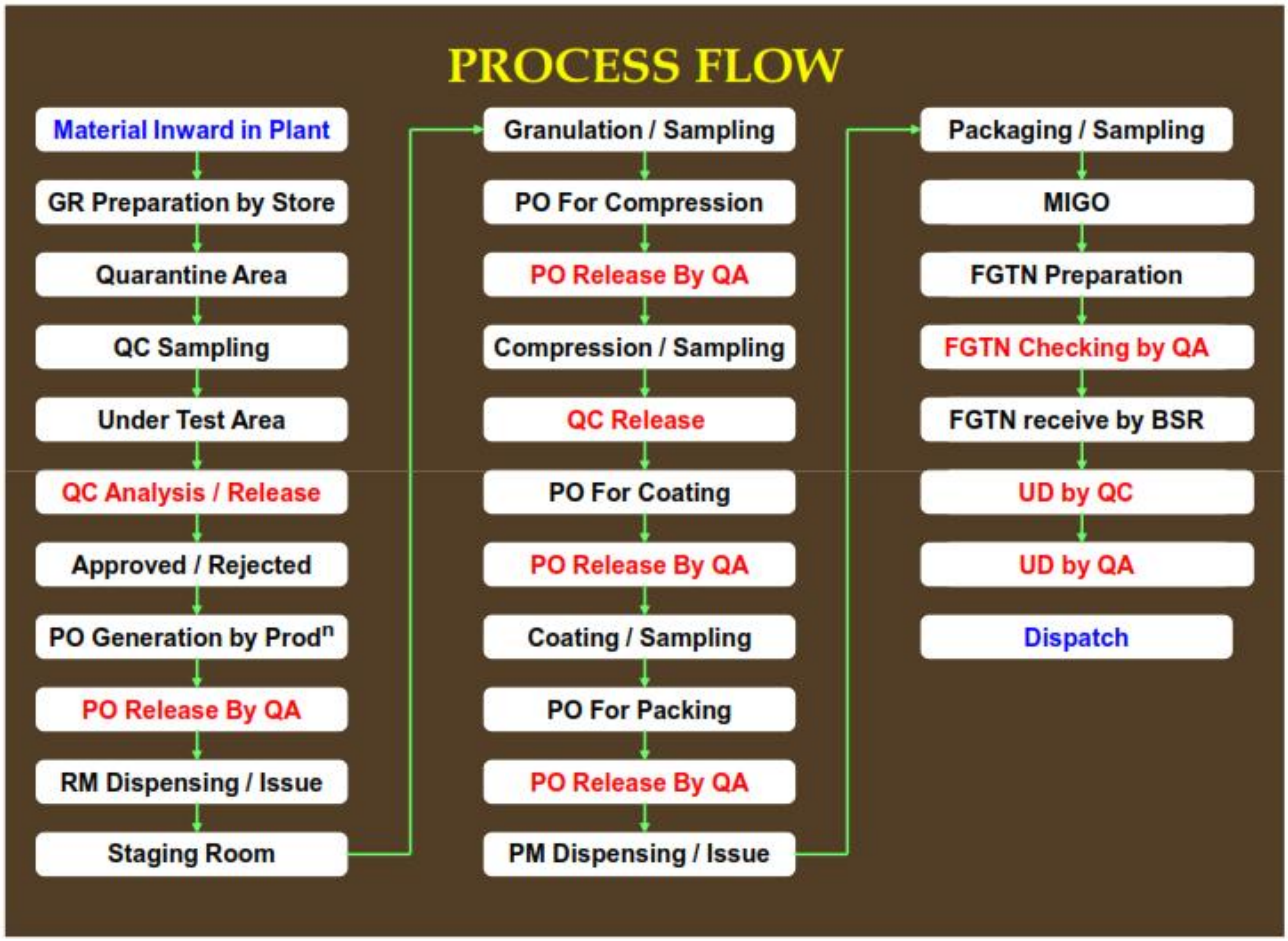
SR. NO.	QUESTION ANSWER
53.0	**SAP**
	SAP stands for Systems, Applications and Products in Data Processing. SAP is used by companies to plan, organize, integrate and manage their various operations like accounting, finance, manufacturing and human resources. The main aim is to improve efficiency and accuracy. SAP is based on server design and uses a relational database to track all information related to a company. It is made up of small programs called transactions. Related transactions together into groups and call them modules. Thus a module is a set of transactions that deal with the same area of business functionality. SAP ECC 5.0 computerizes the functions in the following departments: • Inventory • Procurement • Production Planning • Quality Management • Sales Order Management
53.1	

PHARMA BOOK

SR. NO.	QUESTION ANSWER

SAP ECC 5.0 consists of a set of commercial software programs (called modules) that are licensed from SAP ECC 5.0. The table below identifies the standard SAP ECC 5.0 modules that have been installed for Medley's facilities.

Module Name	General Function	QS Impact(s)
MM	Material Management	Yes
QM	Quality Management	Yes
PP	Production Planning and Control	Yes
SD	Sales & Distribution	Yes
HR	Human Resource	No
FI	Finance Management	No



SR. NO.	QUESTION ANSWER
54.0	**HOLD TIME STUDY**

OBJECTIVE

To establish the maximum period for which the bulk blend, compressed tablets, coating solution & coated tablets, can be stored prior to compression, coating & packaging operation respectively, when stored at the specified conditions of temperature and humidity.

RE – QUALIFICATION

Any change in the storage conditions
Change in formulation

BULK BLEND

Withdraw approximately 300gm of blend for chemical analysis and blend equivalent to 60 gm for microbial limit test and store in sample polybag in an SS container. The lubricated blend can be stored for a maximum period of 60 days. The containers shall be closed properly and labelled adequately and store at granule quarantine area at Temperature 25 ± 2ºC & Relative Humidity 55 ± 5%.

54.1

Collect 100gm of blend for chemical analysis & 20gm for microbial analysis, carry out the sampling after 15 Days, 30 Days and 60 Days of the storage and sample shall be analyzed as per test given in below mention sampling plan.

Sr.No.	Time of testing intervals	Test to be performed
1.	15 ± 2 days	Description, Assay, LOD, Microbial Limit Test
2.	30 ± 2 days	Description, Assay, LOD, Microbial Limit Test
3.	60 ± 2 days	Description, Assay, LOD, Microbial Limit Test

SR. NO.	QUESTION ANSWER

COMPRESSED TABLETS

Withdraw approximately 300 tablets for chemical analysis and tablets equivalent to 60 gm for microbial limit test and store in sample polybag in an SS container. The compressed tablets can be stored for a maximum period of 150 days. The container shall be closed properly and labelled adequately and store at tablet quarantine area at Temperature 25 ± 2ºC & Relative Humidity 55 ± 5%.

Collect 100 tablets for chemical analysis & tablets equivalent to 20gm for microbial analysis, Carry out the sampling after 90 Days, 120 Days and 150 Days of the storage and sample shall be analyzed as per test given in below mention sampling plan.

Sr.No.	Time of testing intervals	Test to be performed
1.	90 ±2 days	Description, Assay, Related Substances, Microbial Limit Test.
2.	120±2 days	Description, Assay, Related Substances, Microbial Limit Test.
3.	150 ±2 days	Description, Assay, Related Substances, Microbial Limit Test.

COATING SOLUTION PREPARATION

Withdraw approximately 150 ml of coating solution and store in a sterile SS container.

Carry out the sampling of the coating solution (30 ml) at initial, 24 hour, 48 hour and 72 hours of storage as per the in-process sampling procedure and analyze the samples as test given in below mention sampling plan.

Sr. No.	Hold time Sample After	Test to be performed
1.	Initial	Total aerobic microbial count, Combined Yeast & mould count, Pathogens
2.	24 Hours	Total aerobic microbial count, Combined Yeast & mould count, Pathogens
3.	48 Hours	Total aerobic microbial count, Combined Yeast & mould count, Pathogens
4.	72 Hours	Total aerobic microbial count, Combined Yeast & mould count, Pathogens

Simpal Baria

SR. NO.	QUESTION ANSWER

COATED TABLETS

Withdraw approximately 300 tablets for chemical analysis and tablets equivalent to 60 gm for microbial limit test and store in sample polybag in an SS container. The coated tablets can be stored for a maximum period of 150 days. The container shall be closed properly and labelled adequately and store at tablet quarantine area at Temperature 25 ± 2ºC & Relative Humidity 55 ± 5%.

Collect 100 tablets for chemical analysis & tablets equivalent to 20gm for microbial analysis, Carry out the sampling after 90 Days, 120 Days and 150 Days of the storage and sample shall be analyzed as per test given in below mention sampling plan.

Sr.No.	Time of testing intervals	Test to be performed
1.	90 ±2 days	Description, Assay, Related Substances, Microbial Limit Test, Dissolution.
2.	120±2 days	Description, Assay, Related Substances, Microbial Limit Test, Dissolution.
3.	150 ±2 days	Description, Assay, Related Substances, Microbial Limit Test, Dissolution.

HOLD TIME STUDY VALIDATED TIME:

Sr.No.	Stage	Validated Time
01	Blend	60 Days
02	Compressed Tablets	150 Days
03	Coating Solution	48 Hours
04	Coated Tablets	150 Days
05	Filled Capsule	150 Days
06	Bulk Liquid	05 Days

SR. NO.	QUESTION ANSWER
55.0	**MVTR**
55.1	**MVTR** MOISTURE VAPOUR TRANSMISSION RATE **OBJECTIVE** To determine the moisture-permeation characteristics of the packaging system being utilized for the packing of unit dose products To evaluate and qualify the suitability of the packaging of products with the USP classification scheme to evaluate the moisture-permeation characteristics of single-unit and unit-dose packs as equipment and operator performance may affect the moisture permeation of a pack. To provide a high degree of assurance that the packaging system being utilized for the packing of unit dose products are meeting the Good Packaging Practices. **RE-QUALIFICATION CRITERIA** Change in packing material and or packing change part such as blister forming/sealing roller components. Change in process parameters. **METHODOLOGY** **Preparation of Desiccant** Dry the desiccant tablets at 110° for one hour prior to use. Use tablets weighing approximately 400 mg each. (If necessary due to limited unit dose container size tablet weighing less than 400mg can be used). **Procedure** Seal a sufficient number of blister strip (not less than 4) with a total of not less than 10 unit-dose blisters are tested with 1 pellet in each unit are tested. Seal a corresponding number of empty packs, each pack containing the same number of unit-dose blisters as used in the test packs, to provide the controls. Store all of the pack at 75 ± 3% relative humidity and at a temperature of 23 ± 2°C. After 24 hours and at subsequent interval specified, remove the packs from the chamber, and allow them to equilibrate for about 25 minutes. Record the weights of the individual packs and return them to the chamber. Weigh the control packs as a unit and divide the total weight by the number of control packs to obtain the average empty pack weight.

SR. NO.	QUESTION ANSWER

Calculate the average rate of moisture permeation in mg per day for each unit-dose blister in each pack taken by the formula.

$$(1 / NX)[(W_F - W_I) - (C_F - C_I)]$$

Where,

N : is the number of days expired in the test period (beginning after the initial 24-hour equilibration period);

X: is the number of separately sealed units per pack;

$(W_F - W_I)$: is the difference in mg between the final and initial weights of each test pack;

$(C_F - C_I)$: is the difference in mg between the average final and average initial weights of the control packs the rates being calculated to two significant figures.

[NOTE: If any indicating pellets turn pink during the procedure or if the average pellet weight increase in any pack exceeds 10% terminate the test and regard only earlier determinations as valid.]

ACCEPTANCE CRITERIA AND CLASSIFICATION OF PACKS

Class A: if no pack tested exceeds 0.5 mg per day in average blister moisture permeation rate; Test period: 28 days.

Class B: if no pack tested exceeds 5 mg per day in average blister moisture permeation rate; Test period: 7 days.

Class C: if no pack tested exceeds 20 mg per day in average blister moisture permeation rate; Test period: 48 hours.

Class D: if the packs tested meet none of the above average blister moisture permeation rate requirements. Test period: 24 hours.

SR. NO.	QUESTION ANSWER
56.0	**LABORATORY DISCREPANCY**
56.1	All laboratory incident should require investigation and documentation. The source of incidents / discrepancies includes but not limited to the following examples; • System suitability failing during High Performance liquid Chromatography (HPLC), Gas Chromatography (GC) etc. • Wrong integration or integration not properly • Known Laboratory Error: This type of an incident is an error that is known to be caused by the analyst (such as a spill) or laboratory instrument failure. • Analysis Carry over observed. • Chromatography–Ghost peak/peak splitting observed. • Any Extraneous peak observed • HPLC/GC system interruption due to leakage problem, connectivity problem and power failure. • Virus attack in software or corruption of software, erratic operation system. • Mistake in calculation and in reporting. • Wrong labelling of sample/improper transfer of sample and sonication • Entry miss in logbook • Any contamination during sample / standard preparation / storage of sample. • Usage of Instrument before calibration etc (by mistake). • Glassware breakage with sample or standard during preparation. • Sample spills during the test for e.g. Loss on drying, Sulphated Ash or water content. • Power failure or power fluctuation during instrumental analysis or microbial analysis. • An unexpected or unplanned event happened in/out side of the laboratory. This type of an event includes, but is not limited to: ➢ Damaged Samples ➢ Power outages or variances ➢ Environment condition out of limit Whenever any Incidence/discrepancies is observed, the analyst/reviewer shall intimate to section incharge, Based on the review of incident, section incharge intimate to QA for login in laboratory incident register and for issue of incident report. Based on the request of section incharge, QA person shall enter the details of incident in laboratory

Simpal Baria

SR. NO.	QUESTION ANSWER
	Incident Register and issue the incident report to QC for investigation. The analyst / reviewer shall write the brief of incidence in the incident report and shall attach all relevant data with report. The Section incharge / Head of the department shall evaluate the incident and suggest the brief corrective action with justification in the incident report. After investigation, conduct re-analysis through a re-issuance of raw data sheet if applicable. For the root cause investigation, Investigation tools can be used during the investigation of incident as per SOP No. QAD 092 "Failure investigation and root cause analysis" where the probable cause not apparent. The analyst shall report the result obtained and shall attach all relevant data generated during the corrective action. Head of the department shall give the preventive action (if any) in the incident report. After completion of QC part, incident report shall be forwarded to quality assurance department, The Head-QA/Designee shall review the incident, other detail and recommended for additional investigation if required and give his/her decision on approval of incident. Under appropriate circumstances corrective and preventive actions must be completed prior to resumption of laboratory related activities that directly impact product quality. Corrective and preventive action commitments are complete upon verification by the Quality Assurance Unit. The section incharge shall take approval of the incident report within 30 working days unless the Quality control manager takes an approval from head QA for an extension of investigation period of incident as per Annexure-III. The reasons or justification for any extension will be documented. In case where peak response is high and results is not in predetermine specification then it shall be reported through a SOP No. QCG 034 "handling of out of specification results". Trend of laboratory incidence shall be analysed monthly.

SR. NO.	QUESTION ANSWER
57.0	**CONTRACT TESTING LABORATORY**

Contract Testing Laboratory:
Laboratory which is situated outside of the premises of Medley Pharmaceuticals Limited, Daman and authorized by Medley with CONTRACT for analysis of the sample.

Selection of Contract Testing Laboratory
Head Quality Control / Head QA / CQA shall identify the contract testing laboratory for analysis of Raw material, Packing Materials, Intermediates , Finished products, Stability Samples and other tests required to be done in contract testing laboratories when required.

The sample may be sent to contract testing laboratory in the following cases:

- In-house testing facility is not available.
- Comparative study is when required.
- Regulatory/Customer's requirement for outside testing.
- Failure of any instrument or non-availability of any instrument, reagent or standards.

For analysis of all Raw Material, intermediate, Finished Product, stability samples and packing material, Contract Testing Laboratory must be approved by local FDA and NABL.

Selection of contract-testing laboratory based on the requirement of the test and availability of the expertise as per the technical requirement and Initial registration of contract testing laboratory through a registration questionnaire for contract testing laboratory

CONTRACT GIVER (CG) shall forward registration questionnaire to CONTRACT ACCEPTOR (CA) for detail information of laboratory. CA shall fill registration questionnaire and return back to CG. On receipt registration questionnaire from CA, CG shall review registration questionnaire and detail information of laboratory.

After receipt of satisfactory detail information of CA, CG shall carry out audit of the respective contract testing laboratory facility as per audit checklist to assess their technical & analytical capability.

Head QC and Head QA / CQA shall plan and carry out contract testing laboratory audit to confirm the compliance level of cGMP and GLP. The auditors should at least have five year's industrial experience in the laboratory function and the auditor must be experienced enough to assess the laboratory and auditor shall be qualified.

Contract testing laboratory audit check list (**Annexure I**) shall be used during the audit, but the audit may be extended to the points given in the check list or as per requirement. Audit findings shall be categorized into Critical, Major and Minor depending on the nature of the observations.

Audit report shall be sent to the auditee for compliance of the observation noted during audit.

Head QA/CQA shall approve the contract testing laboratory based on compliance report received from

SR. NO.	QUESTION ANSWER
	CA. In case compliance report is not satisfactory, carry out re-audit and approve / reject the same based on re-audit observation. The audited contract testing laboratory should have to submit their compliance report within 30 days of time after receipt the audit report from CG. Upon the approval of the contract testing laboratory, a technical agreement shall be made between the CONTRACT GIVER (CG) and CONTRACT ACCEPTOR (CA). If the contract testing laboratory has been rejected, alternate shall be explored. Review the performance of the contract testing laboratory every three years ± three months of the due month. **Technical agreement procedure** The agreement shall be prepared as per the guidance given in (**Annexure -II**) but not limited to, if any further details required same shall be captured. **Approval of agreement** Agreement shall mutually agreed document and shall be signed by both (CG and CA). Agreement shall be reviewed once in every 3 years or as and when required and shall be amended accordingly by both parties Results of a test from contract testing laboratory shall be communicated in writing either through electronic system or hard copy. No verbal communication shall be entertained in this regard.

SR. NO.	QUESTION ANSWER
58.0	**RELEASE OF INTERMEDIATE AND FINISHED PRODUCTS**
	Release: Release is the process of accepting the material if it complies to meet established/approved specification. **Release of semi finished goods (SFG stage)** The following shall be considered as semi finished stage for the respective dosage form. **Lubricated Blend** : Completion of blending stage **Uncoated Tablets** : Compressed Tablets **Coated Tablets** : Completion of Coating stage. **Capsules** : Completion of filling operation. After completion of the respective SFG stage of a batch, Production Officer/Designee shall update the lot quantity in SAP using the transaction code MIGO. After completion of SAP entry, Production shall intimate to IPQA for sampling of SFG stage. IPQA person shall be carried out sampling as per SOP No. QAD 011 “Sampling procedure for In-process and Finished Product”. IPQA shall send sample to QC for testing along with intimation. QC shall perform the finish product analysis at Semi Finished stage.
58.1	QC personnel shall use the transactions QPR4 for sampling and transactions QE51N for result recording as per SOP No.QCG 146 “Sample Drawing and Result Recording of Finished Products ” . Usage decision shall be done by Head-QC/Designee for Semi Finished Goods (SFG) using transaction code QA 11 as per SOP No.QCG 149 “Usage Decision of Finished Products ”. **Batch Production Record (BMR/BPR) review**: On completion of the batch, Production officer/Designee shall update the packed quantity of finished goods (FG) in SAP, using the transaction code MIGO. Production officer/Designee shall prepare the 'Finished Good Transfer Note' in duplicate. The FGTN shall be signed by Production officer/Designee and shall be submitted to Manager-Production/Designee along with complete batch production record. The completed BPR shall be reviewed by Production Manager/Designee, signed at “BPR checked by” column and submit it to IPQA for review along with FGTN in duplicate duly signed in “Checked By” column as an intimation of material transfer from Production to FG stores. IPQA Officer shall review the BMR/BPR as per "Batch Production Record review check list"

SR. NO.	QUESTION ANSWER
	Review of Certificate of Analysis and RDS: Section incharge/Designee shall prepare the COA as per SOP No. QCG 018 "Preparation of Certificate of Analysis". The COA shall be signed by Section incharge/Designee at 'Prepared By' column, Head QC/Designee at "checked by" column. Section incharge/Designee shall send the COA along with Raw Data Sheet and all relevant documents to Head-QA/Designee for approval along with the checklist of analytical records as per **Annexure II**. Head-QA/Designee shall verify the COA against specification and analytical results recorded in RDS, availability of all raw data as per checklist and sign the checklist of analytical records in the 'Checked by' column. Head-QA/Designee shall ensure prior to signing the COA that any OOS result obtained has been investigated and closed as per SOP QCG 034 on 'Handling of out of Specification (OOS) test result". If any discrepancy (Non data based) is observed in COA / RDS, it shall be forwarded to Quality Control department for compliance. On receipt of corrected COA / RDS, Head-QA/Designee shall cross check the rectified discrepancies and sign at "Approved by" column in COA. **Finished Goods Release** Once the BPR and COA is reviewed, Head-QA/Designee shall sign the "BPR review check list" as per annexure I in verified by column and put this remark as " Batch is Released" or "Batch is not Released" by putting "√" mark on the respective column in the checklist. Head-QA/Designee shall give the Usage decision of inspection lot in SAP using transaction code QA 11 as per SOP No. QAD 070 "Usage decision & stock posting of finished products in SAP" for further movement. Head-QA/Designee shall prepare and approve the Certificate of Conformance (COC) as per annexure-IV or Quality certificate as per annexure-V whenever required as a certification that the batch is manufactured, packed & tested complying with cGMP. One copy of the COA & COC shall be attached to BPR. Head-QA/Designee shall forward the COA and COC or Quality Certificate to FG Store for further dispatch process. If the product is "Not Released", investigation shall be carried out. The batch quantity shall be transferred to block stock and stored at a designated place till its decision.

PHARMA BOOK

SR. NO.	QUESTION ANSWER
	COC CONTENTS : Name of Product Finished Product Code, Importing Country Marketing Authorization Number/ Product License No. Strength/ Potency, Dosage Form Package Size and type, Batch No. Date of Completion of Packing, Dispatched Quantity Batch Manufacturing Record No., Batch Packaging Record No. Date of Manufacturing Expiry Date Name, Address and Authorisation number Manufacturing Site Quality Control Site Standard Testing Procedure No. Release Specification No. API Source Finished Product Analytical Raw Data Sheet No. Analytical Report Number a. Certificate of GMP compliance b. Eudra / MHRA GMP Reference Number Results of Analysis, Storage Condition Comments (If Any) [ ] Deviation / [ ] OOS Certification Statement, Person Authorizing for Batch Release Name and position, Signature and Date Verified By Head QA, Signature / Date With Seal **Partial release of finished product**: On packing of a batch, Production Officer shall complete the BPR up to that stage. Production Officer shall create the partial lot to be released in the SAP and inform to QA and partial quantity of batch shall be released for dispatch After analysis, the partial lot of the batch shall be approved and released. The remaining quantity of batch shall be released (when required) after the creation of new inspection lot. Re-analysis of the remaining lot shall be carried out if required by customer. In case where re-analysis of the remaining lot is not required, the initial analysis data shall be entered by QC in result recording transaction in SAP for remaining lot. The remaining lot shall be released for dispatch **In case of SAP failure the following procedure to be followed** Head- QA/Designee shall manually prepare the “Finished Good Release Note” as per Annexure-III. A copy of the release note shall be forwarded to FG Store along with COA and other required documents if any. Finish product release for the market distribution must comply with the requirement of the dossier.

SR. NO.	QUESTION ANSWER

59.0	FAILURE INVESTIGATION AND ROOT CAUSE ANALYSIS
59.1	An **Investigation** is a deviation report, which has been identified as requiring more in depth investigation with the involvement of different functional departments. **Root Cause Analysis:** Root Cause Analysis is a problem solving technique for identifying the basic or cause factor(s) that underlie the occurrence or possible occurrences of an adverse event in a process similar to diagnosis of disease, with the goal always in mind of preventing reoccurrence. Failure Investigation and Root Cause Analysis shall be carried out when a product does not meet the predetermined specification. Failure is defined as any confirmed out of specification (OOS). The Root Cause Analysis is aimed at first generating possible root cause for the problem and then narrowing focus into the most probable cause for the problem. Whenever the failure is identified in the product the same shall be brought to the notice of Head-QA or designee. Failure Investigation and Root Cause Analysis shall be initiated by concerned department along with QA person. QA head will nominate the team for investigation. The documentation shall be done in failure investigation report. Carry out Failure Investigation and Root Cause Analysis using the checklist, but it will not be limited to this checklist and all efforts will be directed to find out the root cause of the failure. Use additional sheets for completing the investigation whenever required. The investigation shall be extended to all the batches / products which could have possible been affected by the failure. Quarantine any Component(s) / Bulk products / Finished Product which might have been affected by the failure till investigation is completed and decision is made. Initiate this action through QA. The investigation may include additional testing of the involved batches / products or components. **Investigation Steps:** It is the responsibility of the department, where the problem originated, to involve in the investigation in consultation with the QA Department to ensure adequacy of the investigation. The failure Investigation and Root Cause Analysis is aimed at first generating possible root cause for the problem and then narrowing focus into the most probable cause for the problem. The Failure Investigation and Root Cause Analysis is done after an event has occurred. It can be used for preventing problems from occurring.

SR. NO.	QUESTION ANSWER
	Investigation team shall perform the investigation using the tools and technique and investigation checklist. **INVESTIGATION TOOLS:** Based on the information available, identify the probable cause for the non-conformance. If the probable cause is not apparent, use following four techniques but not limited to, The **First Technique** to be used for any kind of investigation is **"Genchi Genbustu"**. The meaning and procedure of this technique is mentioned below. **"Genchi Genbustu"** Technique: Means 'Go, and see i.e go and see yourself to thoroughly understand the situation. Define the problem in detail. Include who, what, when, where and how. Briefly describe why the event is a problem. This should be a statement of facts. Ask five "W" and one "H" as mentioned below, a) **W**hat? b) **W**here? c) **W**hen? d) **W**ho? e) **W**hy? f) **H**ow? 1. Observe the problem / situation first hand, personally (not to rely on the report of other). 2. Talk to those at the sharp end (counselling). 3. Explore the contributing visible and invisible factors. 4. Analyze each factor and conclude probability.

SR. NO.	QUESTION ANSWER

The **Second Technique** i.e. **"Brainstorming"** may be used to identify the root cause of the problem. The details of Brainstorming are mentioned below.

Brainstorming: One of the creative problem solving method that allows the people to come-up with suggestion / ideas that could solve the problem or help to identify the root cause of the problem.

1. A meeting with Cross Functional team may be called to brain storm on problem / situation.
2. Relevant people shall ask to think and share their views / suggest ideas to overcome the problem.
3. All views and suggestions shall analyse to identify the cause of problem.

Third Technique i.e. **5 -WHY technique** may be used to identify the cause of problem as per the steps mentioned below.

Five –WHY Technique: It is questions based technique and shall be used for the each possible factor identified for problem. Question shall ask to the right person in right way at right time and place.

1. Take the problem statement and ask question "WHY did that happened?"
2. For each cause, ask the next "WHY did that happened?"
3. Repeat question until the primary cause identified.
4. The cause, when identified should preclude recurrence of the identified non conformance.

Fourth technique **"Six-M Framework" (Ishikava diagram)** using **Fish bone** diagram may be used to identify the root cause of the problem. The steps to use **"Six M framework"** are given below.

Pictorial presentation of fish bone diagram (Refer **Annexure-II**) of Root cause analysis includes,

Head of Fish: Problem of Effect

Bones of the Fish: "Six –M" i.e. Major Causes: Man, Machine/Equipment, Material, Method/Process Measurement and Environment/Mother Nature etc. More groups can be added, if necessary.

Sub-branches: Sub causes

SR. NO.	QUESTION ANSWER

Define your problem from the following source:

Internal: OOS Reports, Self Inspection, Deviations, Trend analysis, FMEA, Annual Product Quality Review.

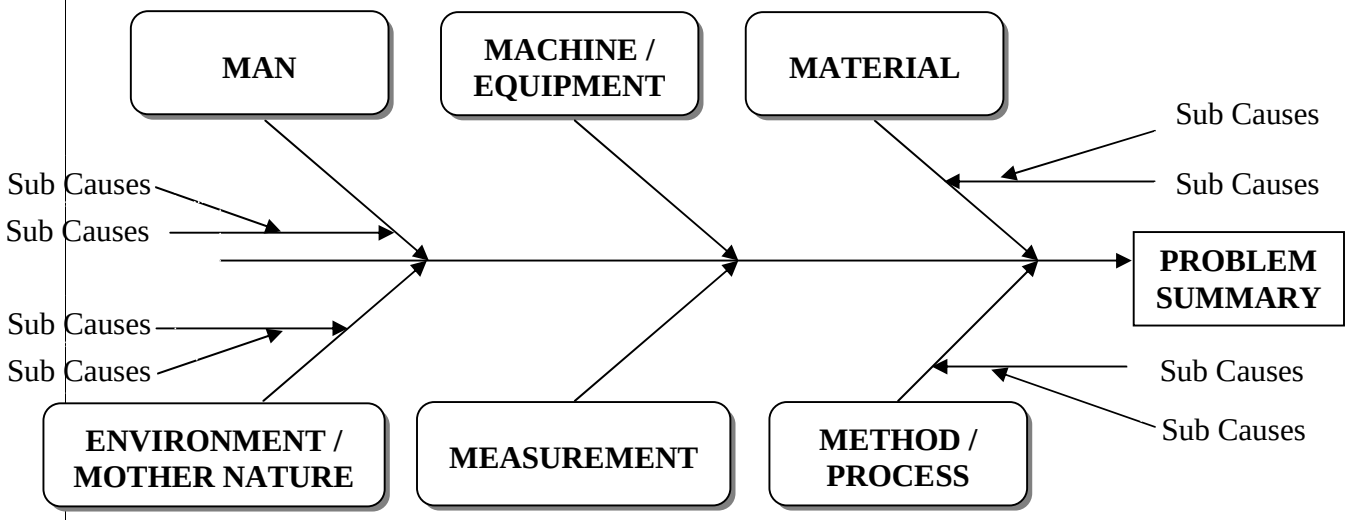
External: Market Complaints, Quality / Regulatory Audit Reports etc.

Root Cause Analysis team should involve those who are most familiar with the processes and systems and include participation of the Department Head, Quality Assurance.

Label each "bone of the fish". The major categories typically utilized are: Man, Machine/Equipment Material, Method/Process, Measurement and Environment/Mother Nature.

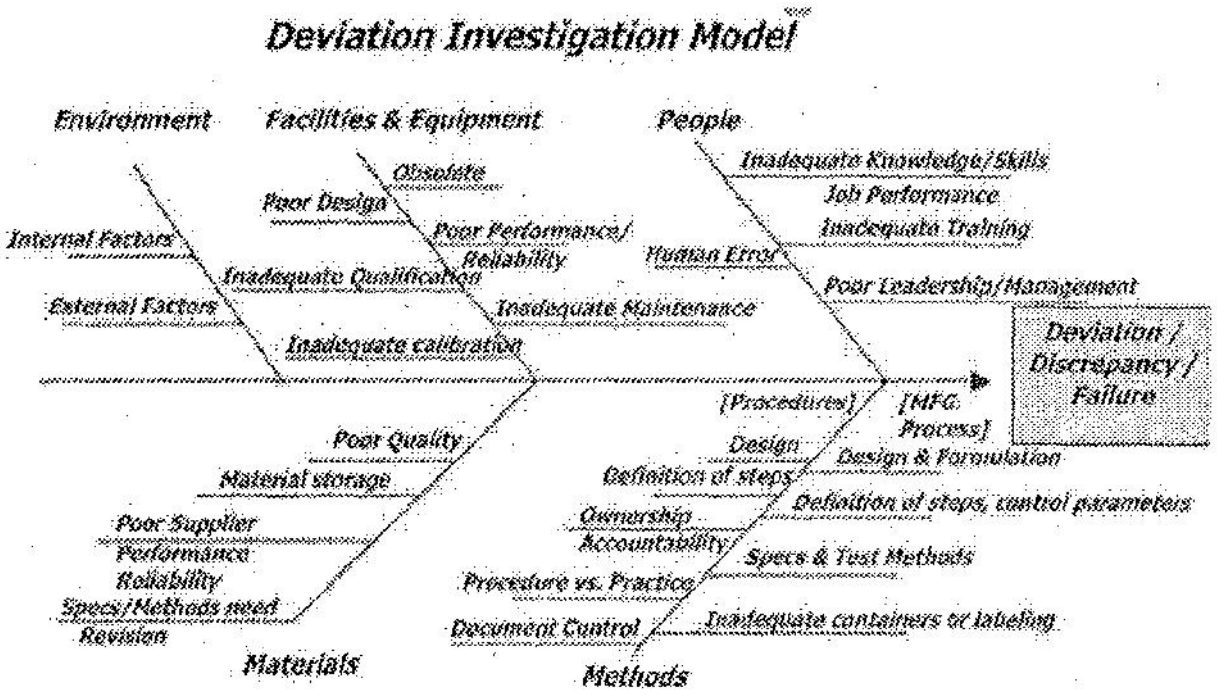
The team should identify probable causes, these could be Man, Machine/Equipment, Material Method/Process, Measurement and Environment/Mother Nature.

FISH BONE DIAGRAM / ISHIKAWA DIAGRAM / CAUSE AND EFFECT DIAGRAM



SR. NO.	QUESTION ANSWER

Example of Fish-bone Diagram:



Analyze the information and identify the actual or hypothesis. Analysis of data must be objective and logical.

Determine the extent of the problem. Is this an isolated occurrence limited to one batch or is this a recurring or potentially system related problem. Evaluate the effects on other processes, products and batches related to the similar problem.

Propose actions and recommendations for the affected batch(s). Evaluate the following aspect of the batch:

- Quality Aspects such as product safety and integrity, product purity and efficacy, product stability, customer perception and potential complaints.
- Regulatory Aspects such as deviations from product registration commitments.
- Compliance Aspects such as non compliance of GMPs, or deviations from revalidation / re-qualification requirements.

If an idea fits on more than one branch place it on both, be sure that the causes have a direct, logical relationship to the problem or effect stated at the head of the fish bone. Continue until potential root cause has been identified. A root cause is one that can explain the “Effect” and if removed would eliminate the problem.

Example for Causes / Reasons of non conformance that may be identified by performing investigation is as per **Annexure-III**.

PHARMA BOOK

SR. NO.	QUESTION ANSWER

1. MATERIAL

- Defective material, Wrong item for use
- Contaminated Material, Wrong specification for use
- Wrong test method (does not evaluate critical material parameters or functionality)
- Outdated material (also see methods), Mix-up in Material
- Inadequate container or storage
- Unacceptable consistency (in or out of specification)
- Unacceptable supplier/manufacturer performance (quality, delivery)
- Material from Unapproved Sources, Outdated material
- Inadequate Container or Storage, Unacceptable consistency

2. MAN

- Inadequate instruction or training, Human error
- Unauthorized to operate, Unskilled and untrained
- Insufficient number of people, Lack of planning
- Inadequate resource allocation, Inadequate communication

3. MACHINE/EQUIPMENT

- Equipment design inadequate or obsolete for use (capacity, tolerance, speed)
- Incorrect tool selection, Out of calibration
- Facility / room / area design not adequate for use (size, environment, finishes)
- Facilities or equipment not qualified, capability is unknown or not documented
- Facility / room / area fails to maintain specifications(also see design)
- Equipment breakdowns (unpredictable); Capability or reliability unknown
- Equipment not calibrated (also see methods)
- Lack of or inadequate facility maintenance (unscheduled/reactive, routine, preventive, or predictive maintenance)
- Lack of or inadequate equipment maintenance (unscheduled/reactive, routine, preventive, or Predictive)

4. METHOD/ PROCESS

- Inadequate design of formulation (stability, functionality)

SR. NO.	QUESTION ANSWER
	➢ Inadequate design of manufacturing process (sequence, timing, complexity) ➢ Wrong or inadequate equipment (also see equipment) ➢ Inadequate definition of steps, critical parameters in batch records ➢ Process science not understood (also see people) ➢ Process is not capable of consistent performance to meet specifications ➢ Process is not adequately validated; critical parameters unknown ➢ Improper process/product test methods and/or specification,No procedure ➢ Inadequate design for use (too complicated, too many patches, does not handle expectation, not fail safe where needed, no feedback or communication loops) ➢ Inadequate definition or unclear/understandable instructions (critical steps to reproduce the task consistently are not defined in the SOP) ➢ Ownership(individual) of the tasks and results are not defined ➢ Accountability for results not accepted (also see people, management) ➢ Inadequate communication of procedure or results (also see design and management) ➢ Results of the procedure/process are not measured/trended/communicated **5. MEASUREMENT** ➢ Procedures not followed, Practices are not the same as written procedures, ➢ Measuring techniques not validated. **6. ENVIRONMENT/MOTHER NATURE** ➢ Weather extremes (temperature, humidity, rain, wind etc.) ➢ Improper monitoring of temperature ➢ Humidity conditions and storage conditions during handling / transportation **7. DOCUMENTS** ➢ Forms missing information, does not reflect task Format confusing and not user-friendly ➢ Obsolete or uncontrolled editions **8. NON-ASSIGNABLE CAUSE** ➢ An assignable cause cannot be determined. Each alternative shall be analyzed and checked for potential relationships between multiple contributory factors. Eliminate alternatives one by one after analysis that could not be the root cause.

SR. NO.	QUESTION ANSWER
	Finally list the probable cause and identify the exact root cause or causes among them Look for those items that appear in more than one category. These become the "most probable causes". 'Human error' can not be an only root cause or primary root cause for any problem. If 'Human error' is identified as a cause of the problem than matter shall be further investigated to identify the root cause to make as error. Root Cause shall be categorized in to any one or more as per categories guided in **Annexure -III** From those items identified as the "Most Probable Causes" the team shall reach a consensus using the team's best collective judgment on listing those items being the "Most Probable Cause". Develop Corrective / Preventive Actions (CAPA) and document them as per SOP No. QAD 042 on "Corrective and Preventive Action" for the affected batch or batches. Develop preventive actions to avoid recurrence. Corrective and Preventive actions must be monitored to completion. Corrective Actions emerged from the investigation shall be taken with proper change control if required, and follow up shall be carried out for all the suggested corrective action(s) as per SOP No. QAD 042 for Corrective Action and Preventive Action. The Failure Investigations and Root Cause Analysis Report shall be signed by the QA, Production and any other department involved. The report shall be forwarded to Head-QA for approval. Head-QA or designee shall take the final decision, based on the investigation findings. The Failure Investigations and Root Cause Analysis Report shall be maintained in QA-documentation cell with all the supporting data. Designated QA person shall allot the Failure Investigations and Root Cause Analysis Report number. A photocopy of investigation report shall be filed in Batch production record of affected batch (es). The Head-QA or designee shall ensure that the corrected action has been implemented as per the findings. The Failure Investigations and Root Cause Analysis shall be completed within 30 working days from the initiating date. If investigation could not be completed within stipulated time, mention justification and tentative time for the completion of investigation and should be addressed through the SOP No. QAD 098 on "Period Extension for Document Closing".

SR. NO.	QUESTION ANSWER
60.0	**HANDLING OF PHARMACOPEIAL CHANGES**
60.1	The Pharmacopeia's and supplements shall be procured by the concerned departments within the shortest possible time of release of the publication. ADL shall prepare and circulate, within 7 working days in the first month of every year, to R&D, site production and quality head/s and CQA the release dates, official dates targeted official publications for • USP/NF and its supplements, • USP-Pharmacopeial Forum (USP-PF), • Ph. Eur. and its supplements, • BP • IP and its addendums. ADL shall assign a unique tracking number for each requirement/changes. ADL shall intimate to CQA for the drug substance, drug Product and excipients of new/revised monographs and new/revised general chapters from USP, BP, EP, IP or any other applicable pharmacopeia; within 10 business days of release / receipt of the respective Pharmacopeial publications, Designated person from CQA shall review the changes and identify the impacted plant /concerned departments and intimate the same for their evaluation within 5 business days of the receipt of intimation from the ADL. The possible changes are listed in but not limited to the Annexure-II and action shall be taken as per annexure-II. Site-Head QA or designee shall review the monograph/ general chapter in co-ordination with plant QC and production. If the existing product/ material comply with the new requirement the same shall be intimated back to Head CQA. In case existing product/ materials does not meet requirements or unable to confirm the compliance due to technical reasons, then QA shall discuss the matter with R&D and CQA to resolve any technical issue. In case of purchased materials, the matter may be referred to Purchase department to co-ordinate with manufacturer of the material. The last three batches material received/ product manufactured shall be considered for evaluation purpose, wherever available. Samples from the control samples of the validation /Exhibit batches, if available will also be included for the comparison study for evaluation of the results obtained by monograph method and those of obtained by In-House method. Whenever applicable, stability samples also shall be evaluated. In case evaluation is inconclusive even after discussion with relevant groups or non compliance to the requirements, the matter shall be referred to R&D through CQA Head in case of manufactured products providing all the evaluation data. In case of purchased materials, the same shall be referred to Purchase

SR. NO.	QUESTION ANSWER
	department for further communication to manufacturer with intimation to CQA Head. R&D shall review the data, which is received from plant and evaluate the product in line with new/revised monograph or general chapter. Report on the suitability of the monograph/general chapter will be made by R&D and same shall be submitted to CQA. Head CQA shall review the suitability studies performed and once found satisfactory, shall communicate to concerned department for implementation through change control procedure. Change control system shall identify the activities and impacted documents due to the change or new requirement. Typically following documents may require revision: Specification, STP's, BMR/BPR, MMD Art work, license update and SAP entries (Item codes/Products codes) as applicable. Any in-house parameter which is part of the existing specification, but is not part of the proposed monograph, the same shall continue to be part of the specification as an in-house parameter. In case of contract manufacturing of formulations, if the evaluation is not feasible at their location then it shall be evaluated at Medley. Location of evaluation (any of Medley's manufacturing location or at R&D) shall be decided by Head-CQA based on the requirements and extent of evaluation in consultation with Contract manufacturing QA. However for the APIs, such evaluation shall be conducted at R&D. A detailed flow chart of activities with indicative timeline is presented in Annexure-IV. Timeline may vary based on the criticality of the change requirement. However, the evaluation shall be completed by the proposed implementation date.

Simpal Baria

SR. NO.	QUESTION ANSWER

61.0 GOOD MANUFACTURING PRACTICES (GMP)

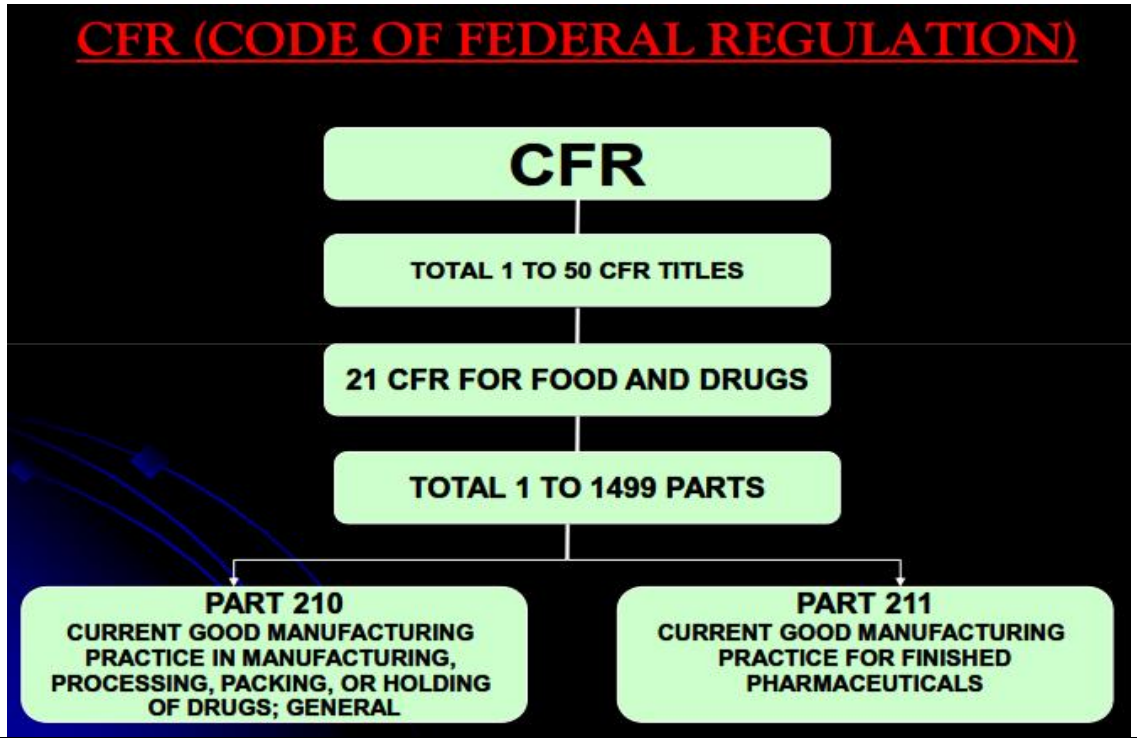
61.1

GMP is Part of quality assurance which ensures that products are consistently produced and control to quality standards appropriate to their intended use and as required by marketing authorization.

GMP was born in Jun 1963 in USA and first guideline on GMP was written and practiced in USA

- Why GMP? It ensures:
  - No process deviations, Consistent quality
  - No product failure, No reprocessing
  - No Product complaint, No Product recalls
  - No inspection failures, No FDA actions
  - Better productivity and therefore, Better profitability, Customer delight
  - Regulatory compliance

SR. NO	COUNTRY	REGULATORY AUTHORITY	FULL NAME
1.	USA	USFDA	United State Food and Drug Administration
2.	U.K	MHRA	Medicines and Healthcare Products Regulatory Agency
3.	AUSTRALIA	TGA	Therapeutic Goods Administration
4.	SOUTH AFRICA	MCC	Medicine Control Council
5.	EUROPE	EMEA	European Medicines Evaluation Agency
6.	UGANDA	NDA	National Drug Authority
7.	ROMANIA	NMA	National Medicines Agency
8.	NIGERIA	NAFDAC	National Agency for Food And Drug Administration and Control
9.	BRAZIL	ANVISA	Agencia Nacional de Vigiloncia Sanitaria
10.	MALAYSIA	DCA	Drug Control Authority
11.	PHILIPPINES	BFDA	Bureau of Food and Drug Administration
12.	VIETNAM	MOH	Ministry of Health
13.	THAILAND	FDA	Food and Drug Authority
14.	SRILANKA	SPC	State Pharmaceutical Corporation
15.	ZIMBABWE	MCA Z	Medicines Control Authority of Zimbabwe
16.	SINGAPORE	HAS	Health Sciences Authority
17.	CANADA	TPP	Therapeutic Product Programme
18.	COLUMBIA	INVIMA	Instituto National de Vigilincia Ministerio de la medicamentos de y Atimentos

SR. NO.	QUESTION ANSWER
62.0	**21 CFR (CODE OF FEDERAL REGULATIONS)**
62.1	❖ CFR is guideline of USA ❖ 21 is no. of USA Rules and regulations. ❖ There are two parts of 21 CFR ❖ 210: Current Good Manufacturing Practices in Manufacturing and Packing ❖ 211: Current Good Manufacturing Practices for Finished Products. ❖ Subpart of 211 Subpart A: General Provisions Subpart B: Personnel and Organization Subpart C: Facility and building Subpart D: Equipment Subpart E: Control of Container and Product closer Subpart F: Process control Subpart G: Packing and labeling control Subpart H: Holding and distribution Subpart I: Laboratory control Subpart J: Records and Reports Subpart K: Return Products 

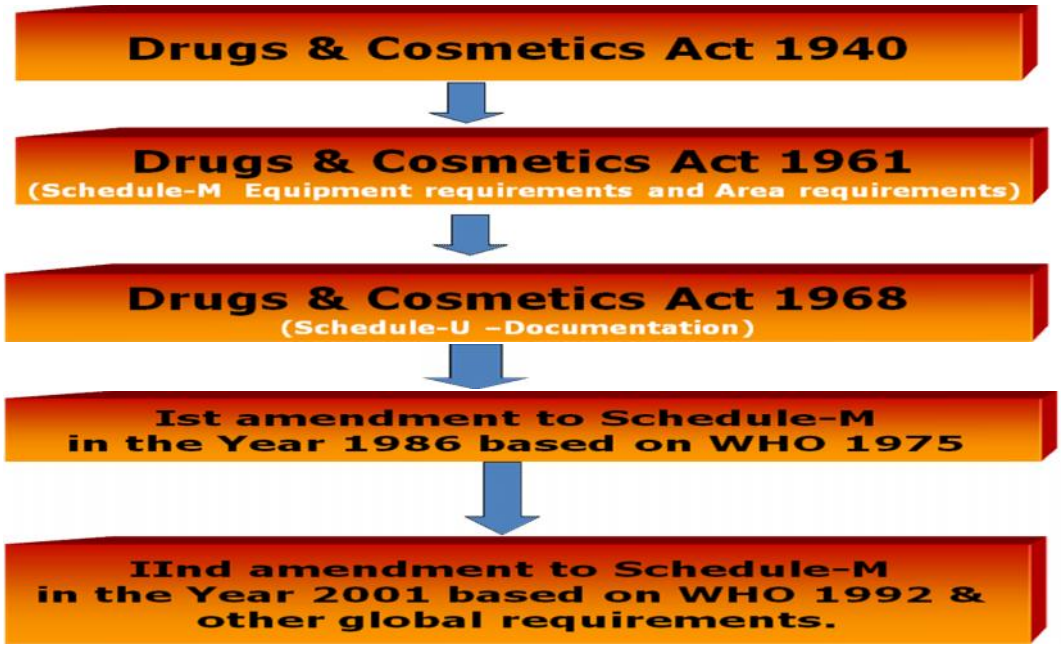
SR. NO.	QUESTION ANSWER
63.0	**ICH (INTERNATIONAL CONFERENCE HARMONIZATION)**
63.1	ICH stands for International Conference On Harmonisation Harmonization process founded in 1990 (US, EU and Japan) There are 4 technical Topics ❖ Quality (Q) ❖ Safety (S) ❖ Efficacy (E) and ❖ Multidisciplinary (M) ❖ ICH Q-Documents Q1. Stability Q2. Analytical Validation Q3. Impurities Q4. Pharmacopeias Q5. Quality of Biotechnological products Q6. Specifications Q7. GMP Q8.Phamaceutical Development Q9. Quality Risk Management Q10. Pharmaceutical Quality System Q11.Development and Manufacture of Drug Substance

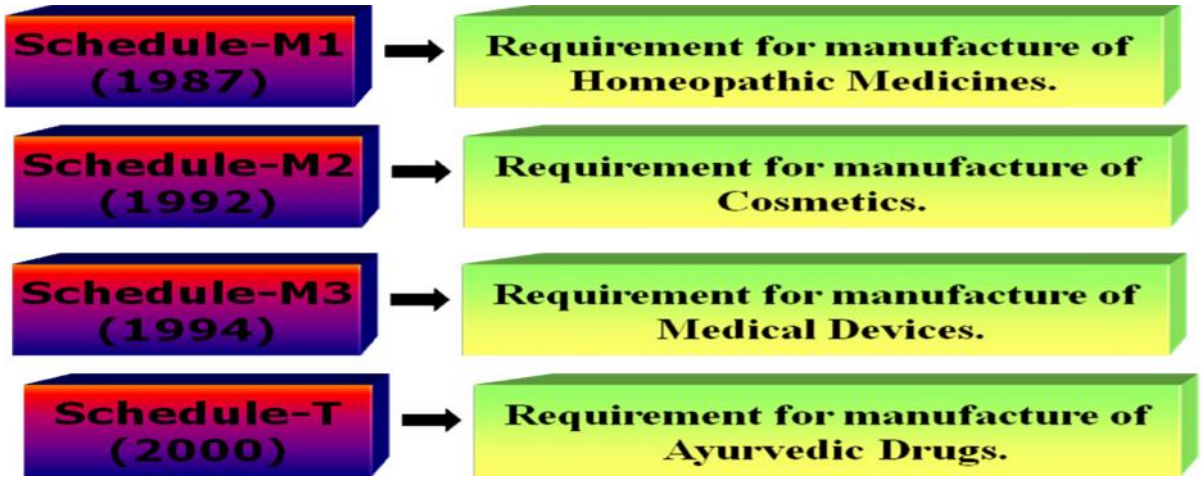
PHARMA BOOK

SR. NO.	QUESTION ANSWER
	DETAILS **Q1A(R2)** Stability Testing of New Drug Substances and Products (Second Revision) **Q1B** Stability Testing: Photo stability Testing of New Drug Substances and Products **Q1C** Stability Testing for New Dosage Forms (Annex to Q1A(R2)) **Q1D** Bracketing and Matrixing Designs for Stability Testing of New Drug Substances and Products **Q1E** Evaluation for Stability Data **Q1F** Stability Data Package for Registration Applications in Climatic Zones III and IV **Q2A** Text on Validation of Analytical Procedures **Q2B** Validation of Analytical Procedures: Methodology **Q3A(R)** Impurities in New Drug Substances (Revised) **Q3B(R)** Impurities in New Drug Products (Revised) **Q3C** Impurities: Guideline for Residual Solvents **Q3C(M)** Impurities : Guideline for Residual Solvents (Maintenance) **Q4** Pharmacopoeias **Q4A** Pharmacopoeial Harmonization **Q4B** Regulatory Acceptance of Pharmacopoeial Interchangeability

SR. NO.	QUESTION ANSWER
	Q5A Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin **Q5B** Quality of Biotechnological Products: Analysis of the Expression Construct in Cells Used for Production of r-DNA Derived Protein Products **Q5C** Quality of Biotechnological Products: Stability Testing of Biotechnological/Biological Products **Q5D** Derivation and Characterization of Cell Substrates Used for Production of Biotechnological/Biological Products **Q5E** Comparability of Biotechnological/Biological Products Subject to Changes in their Manufacturing Process **Q6A** Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances including Decision Trees **Q6B** Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products **Q7A** Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients **Q8** Pharmaceutical Development **Q9** Quality Risk Management **Q10** Pharmaceutical Quality Systems **Q11 (Concept Paper)** Development and Manufacture of Drug Substance

SR. NO.	QUESTION ANSWER
64.0	**SCHEDULE M**
64.1	Schedule M is Schedule of Drugs and Cosmetics Act. Schedule M is basic guide line of Indian Government for Manufacturing of Pharmaceutical Product Good Manufacturing Practices And Requirements Of Premises, Plant And Equipment For Pharmaceutical Products





PHARMA BOOK

SR. NO.	QUESTION ANSWER

TYPES OF SCHEDULE

SR. NO.	SCHEDULE NAME	TITLE OF SCHEDULE
1.	SCHEDULE A	All Forms
2.	SCHEDULE B	Fees for test or analysis by the Central Drugs Laboratories or State Drugs Laboratories
	SCHEDULE B-1	Fees for test or analysis by the Pharmacopoeial laboratory for Indian medicine (PLIM) or the government analysis.
3.	SCHEDULE C	Biological and Special Products
	SCHEDULE C (1)	Other Special Products
4.	SCHEDULE D	Class of drugs Extent and conditions of exemption
	SCHEDULE D(I)	Information and undertaking required to be submitted by the manufacturer or his authorized agent with the Application Form for a Registration Certificate. The format shall be properly filled in for each application in Form 40. The detailed information, secret in nature, may be furnished on a Computer Floppy.
	SCHEDULE D (II)	Information required to be submitted by the manufacturer or his authorized agent with the Application Form for the registration of a bulk drug/formulation/special product for its import into India. The format shall be properly filled in and the detailed information, secret in nature, may be furnished on a Computer Floppy
	SCHEDULE D (III)	Information and undertaking required to be submitted by the manufacturer or his authorized importer/Distributor/agent with the Application Form for a registration certificate. The format shall be properly filled in for each application in Form 42
5.	SCHEDULE-E	List of Poisonous substances (Omitted)
	SCHEDULE-E(1)	List of poisonous substances under the Ayurvedic (including Siddha) and Unani Systems of Medicine
6.	SCHEDULE F	Part I to Part XII-A – Omitted PART XII B - Requirements For The Functioning And Operation Of A Blood Bank And / Or For Preparation Of Blood Components. PART XII C - I. Requirements For Manufacture Of Blood Products II. Requirements for manufacture of blood products From bulk finished products PART XIII - General

SR. NO.	QUESTION ANSWER		
		SCHEDULE F(I)	PART 1–Vaccines PART II –Antisera PART III- Diagnostic Antigens PART IV- General
		SCHEDULE F (II)	Standards for surgical dressings
		SCHEDULE F (III)	Standards for umbilical tapes
		SCHEDULE FF	Standards for ophthalmic preparations.
	7.	SCHEDULE G	List
	8.	SCHEDULE H	Prescription Drugs
	9.	SCHEDULE I	Particulars as to proportion of poison in certain cases (Omited)
	10.	SCHEDULE J	Diseases and ailments (by whatever name described) which a drug may not purport to prevent or cure or make claims to prevent or cure.
	11.	SCHEDULE K	Class of Drugs Extent and Conditions of Exemption
	12.	SCHEDULE L	(Omitted)
		SCHEDULE L 1	Good Laboratory practices and requirement of premises and equipments
	13.	SCHEDULE M	Good Manufacturing Practices and Requirements of Premises, Plant and Equipment For Pharmaceutical Products PART 1 - Good manufacturing practices for premises and materials PART IA- Specific requirements for manufacture of sterile products, parenteral preparations (small volume injectables and large Volume parenterals) and sterile ophthalmic preparations. PART IB -Specific requirements for manufacture of oral solid dosage forms (tablets and capsules) PART IC- Specific requirements for manufacture of oral liquids (syrups, elixirs, emulsions and suspensions) PART ID- Specific requirements for manufacture of topical products , i.e. external preparations (creams,

SR. NO.	QUESTION ANSWER		
			ointments, pastes, emulsions, lotions, solutions, dusting powders and identical products) PART 1E- Specific Requirements for manufacture of Metered-dose- inhalers (mdi) PART 1F - Specific requirements of premises, plant and Materials for manufacture of active Pharmaceutial ingredients (bulk drugs) PART II- Requirements Of Plant And Equipment
		SCHEDUE M-I	Requirements of factory premises for manufacture of Homoeopathic preparations
		SCHEDULE M-II	Requirements of factory premises for manufacture of cosmetics
		SCHEDULE M-III	Requirements of factory premises for manufacture of medical devices
	14.0	SCHEDULE N	List of minimum equipment for the efficient running of a pharmacy
	15.0	SCHEDULE O	Standard for disinfectant fluids
	16.0	SCHEDULE P	Life period of drugs
		SCHEDULE P1	Pack sizes of drugs
	17.0	SCHEDULE Q	PART I -List of Dyes, colours and Pigments permitted to be used in Cosmetics and Soaps as given under IS : 4707 (Part I)-1988 as amended by the Bureau of Indian Standards PART II – List of Colours permitted to be used in Soaps.
	18.0	SCHEDULE R	Standards for condoms made of rubber latex intended for single use and other mechanical contraceptives
		SCHEDULE R1	Standard Medical Devices
	19.0	SCHEDULE S	Standard of cosmetics
	20.0	SCHEDULE T	Good manufacturing practices for ayurvedic, Siddha and unani medicines
		SCHEDULE T1	Form for record of utilization of raw material by ayurvedic, Siddha and unani licensed manufacturing units during the financial year
	21.0	SCHEDULE U	I. Particulars to be shown in Manufacturing Records II. Records of Raw Materials III. Particulars to be recorded in the Analytical Records

SR. NO.	QUESTION ANSWER		
		SCHEDULE U(I)	I. Particulars to be shown in the manufacturing records: II. Records of raw materials:
	22.0	SCHEDULE V	Standards For Patent Or Proprietary Medicines
	23.0	SCHEDULE W	(Omitted)
	24.0	SCHEDULE X	List
	25.0	SCHEDULE Y	Requirements And Guidelines For Permission To Import And / Or Manufacture Of New Drugs For Sale Or To Undertake Clinical Trials
65.0	**VARIATION FILE**		
65.1	**WHAT IS VARIATION:** The legal definition relating to variation to the terms of Marketing Authorisations (MAs) is: "an amendment to the contents of the documents referred to in Articles 8 to 12 of Directive 2001/83/EC" Articles 8 to 12 provide a list of the documentation to be submitted and ultimately approved for any Marketing Authorisation Application (MAA). Once an MA has been granted, the Marketing Authorisation Holder (MAH) has a legal obligation to ensure that the licence is kept up-to-date as the approved particulars evolve over time. The key procedure for managing such changes is the EU Variations procedure. A variation application basically details a proposed change to approved documentation, providing a formal means by which the approved licence details held by the Member State Competent Authorities (CAs) for a given medicinal product can be updated. **WHAT ARE THE LEGISLATION AND GUIDELINES GOVERNING VARIATIONS IN THE EU?** The European variations regulations were revised relatively recently and new rules (EC Regulation 1234/2008) describing revised variation details (e.g. variation types, amendment to the default type, provision of submission information for groupings/worksharing, implementation, etc.) came into force as of 01 January 2010. In adition to EC 1234/2008, a key revised document was also published, the so-called, "Variations Classification Guideline" *(Guideline on the details of the various categories of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products 2010/C 17/01)*. This document provides details of the classification of variations, by type and category (see below), for specific defined changes for all sections of the MA dossier (administrative/quality/safety/efficacy/pharmacovigilance).		

SR. NO.	QUESTION ANSWER

Whilst the list of changes provided is not exhaustive, it is designed to be updated periodically as technical and scientific progress is made. It is anticipated that Variations Classification Guideline will evolve over time to capture new and updated types of change, as these are encountered by the CAs/MAHs.

WHAT ARE THE VARIATION TYPES AND CATEGORIES?

Three different variation types are defined by EC Regulation 1234/2008, with intrinsic varying implications for the type and complexity of the change(s) covered by each and the likely impact of the change upon the quality, safety or efficacy of the product:

Type IA/IAIN: these are so-called, "Do and Tell", minor variations, which have only a minimal impact, or no impact at all, on the quality, safety or efficacy of the medicinal product concerned (N.B.: IAIN – Type IA change requiring 'Immediate Notification' to the CAs.). It should be noted that, by their very nature, these changes must have been implemented prior to notification of the change to the CAs;

Type IB: these are so-called, "Tell, Wait and Do", and are minor variations which are not otherwise classified as minor Type IA variations or major Type II variations (or extensions). Type IB is now the 'default' category (superseding the 'old' Type II default);

Type II: major variations, which are not an extension, and which may have a significant impact upon the quality, safety or efficacy of the medicinal product concerned.

The Variation Classification Guideline specifies a list of variation categories for different types of changes to the MA dossier that are frequently proposed by MAHs. For each variation category, the Guideline indicates (if applicable) the relevant conditions that must be met to be valid, the documentation that should be supplied to support the change, and the appropriate variation type (IA/IAIN, IB, II) under which the submission should be made. For example, a "Change to the specification parameters and/or limits of the finished product" should be submitted under variation category B.II.d.1, sub-category a) to g), as a Type IA/IAIN, IB or II, depending upon the exact nature of the change/circumstances, and the applicant's ability to meet the submission conditions/document requirements, as defined by the Guideline.

The variation application form also specifies an additional category, "z) other variation", for changes that are not foreseen by the Guideline.

WHAT DOCUMENTATION NEEDS TO BE SUBMITTED WITH A VARIATION?

In summary, the core components of a variation package to be submitted to the CAs must include:

A covering letter, stating details of the licence to be amended plus the background to the proposed change(s), etc.

SR. NO.	QUESTION ANSWER
	A completed application form, describing amongst other information: the submission route (national/MRP/DCP/CP); MAH and licence details; the appropriate variation type and category; a description of (and reason for) the change; a comparison of the 'present' licence particulars with those 'proposed' for the change; the fee to be paid (if any); the MAH's declaration that only those changes explicitly included with the variation application have been made; date of implementation of the change(s). Updated product information: SmPC, PIL, other labelling (packaging) details. Specification of the fee(s)/cost(s) for the application and proof of payment (if appropriate). Additional supporting documentation, where required, depending upon the nature of the change to be made, the variation type and category. The above general list is not exhaustive and it should be noted that the overall submission content will be further defined by the type of variation to be submitted and the exact nature of the change(s) to be made. **IS THERE A FEE FOR VARIATIONS?** From a pan-European perspective, the fee structures applied by the various CAs vary widely. For example, in the UK there is no fee for a Type IA variation, but fees are charged for Type IB and Type II variations, whereas in France there is a corresponding flat fee for any type of variation. In addition, some CAs charge reduced fees for grouped applications, whereas others do not, and some CAs (e.g., the Netherlands) charge an annual maintenance fee rather than charging for individual variation submissions. The key message is to recognise that fees may vary widely, depending upon where and how the submission is to be made. In many instances, the likely fee burden may also play a significant role in defining the overall submission structure (and possibly content). It is therefore particularly important to undertake some planning and research into the fees charged by the relevant CA(s) in order to avoid prohibitive submission costs. **HOW SHOULD VARIATION DOCUMENTATION BE PRESENTED?** Many CAs now accept electronic (CD/DVD) only submissions, but it is still important to check each Member State's requirements in this regard. In addition, close attention must be paid to requirements for file naming convention/submission structure (e.g., NeeS/eCTD/Special Mail 5) and numbers of submission copies, as these details may also vary between different Member States. The requirements of the individual CA(s) should be ascertained well in advance of any submission. **HOW LONG DOES ASSESSMENT OF VARIATIONS TAKE?** In principle, the different types of variation (IA/IAIN/IB/II) follow the same assessment timescales following successful validation, irrespective of the type of product licence held (national/MRP/DCP/CP): 1. Type IA/IAIN – 30 days 2. Type IB – 30 days

SR. NO.	QUESTION ANSWER
	3. Type II – 30 days (expedited for safety changes), 60 days (standard) or 90 days (for complex changes for example change to therapeutic indication) In practise there is considerable variation in the actual timescales for any given submission, depending upon which CAs are involved and any particular local assessment that may exist with the CAs at that time. **WHAT ASSISTANCE CAN S-CUBED PROVIDE?** Our highly experienced Regulatory Affairs consultants are fully conversant with the requirements for the preparation and submission of variations, as defined by the new legislation. The S-cubed team has an in-depth knowledge of EU submission procedures and validation requirements. We can assist in avoiding simple, yet all too common, pitfalls that may otherwise result in the costly time and fee penalties that are inevitably associated with rejected submission. In some respects, the new variations legislation appears to have complicated the 'variations landscape'. Various 'grey areas' exist for which no clear direction has thus far been forthcoming from the national CAs/EMA, and these areas of uncertainty vary from EU state to state. In addition to a sound understanding of the formal submission requirements, S-cubed has developed (and continues to develop) a wealth of practical experience and knowledge from a wide range of different clients and through our interactions with the EU CAs. This additional insight has proven invaluable in developing an appreciation of how individual CAs view different aspects of the new legislation, and how local differences in interpretation and implementation might impact upon the success of any given submission. Armed with both the formal guidelines and knowledge of 'what works best' at a local level in different EU member states, S-cubed is ideally positioned to translate this information into pragmatic, efficient and cost-effective variation submission strategies for our clients. To ensure that variation applications are reviewed, assessed and approved with minimal delay, S-cubed can assist clients with the following tasks: **Pre-submission:** document review and gap analysis; definition of the most time- and cost-effective submission strategy; preparation of the submission package (including ghost-authorship of expert statements and arrangement of expert sign-off, if required). **Submission:** S-cubed will either submit the variation package on behalf of the client or provide a submission-ready package for the client to submit themselves. **Post-submission:** should any queries arise from CA review of the variation, S-cubed can formulate written responses to each of the queries within the specified response timeframes and liaise with the CAs, as appropriate, to ensure that submissions avoid rejection and are ultimately approved.

SR. NO.	QUESTION ANSWER
66.0	**CLINICAL TRIALS**
66.1	**WHAT IS A CLINICAL TRIAL?** Clinical trials are required for new active substances or combinations of substances which are intended to prevent or treat a human disease or illness. The purpose of a clinical development program is to assess the pharmacological and pharmacodynamic effects along with the safety and efficacy of an Investigational Medicinal Product (IMP). Clinical trials are conducted so that sufficient data on the safety and efficacy of a new product can be assessed before the product is granted by the regulatory authorities and supplied on the European market. Depending on the type of product and its stage of development, the types of trials conducted range from first-in-man studies for new compounds to studies with products which already have marketing authorisations. Clinical trials are classified into the following phases: **Phase I trials:** These studies enrol only a small number of people (20-80) and are designed to evaluate the safety of a drug, determine a dosage range and identify side effects. **Phase II trials:** These trials are given to larger groups of people (100-300) and are designed to evaluate how well the drug works and to test the safety of the drug. **Phase III trials:** These studies confirm the effectiveness of the drug, compare it to current standards and collect sufficient data to illustrate that the drug can be used safely. **Phase IV trials:** These post marketing studies are used to evaluate a drug's optimal use, side effects, risks and benefits over a longer period of time and in a larger patient population. **WHAT IS A CLINICAL TRIAL AUTHORISATION (CTA) APPLICATION?** In order to conduct a clinical trial in the EU, a Clinical Trial Authorisation must be obtained. A CTA application is submitted to the National Competent Authorities involved in the study or to the Clinical Trials Facilitation Group (CTFG) when the Voluntary Harmonisation Procedure (VHP) is being used. A trial can only start once the CTA has been approved and the Ethics Committee has issued a favourable opinion.

SR. NO.	QUESTION ANSWER
	The following core documentation is required in a CTA application: • Covering letter • Copy of EudraCT number • Clinical Trial Application and valid xml • Protocol • Investigator's Brochure (IB) • Investigational Medicinal Product Dossier (IMPD) – or simplified IMPD • Non-IMP Dossier (if required), Scientific advice Meeting Minutes (if available) • EMA Decision on the Paediatric Investigation Plan (if applicable) • Investigational Medicinal Product labelling (if applicable to the member state) • Proof of payment (if applicable to the member state) • Manufacturer's or Importer's Authorisation • QP declaration • Additional national documents (varies depending on the member states) **What is a Protocol?** A clinical trial protocol is a document that outlines the key parameters and study plan for the proposed clinical trial. The protocol document outlines the objectives (primary and secondary), study design, dosing, inclusion/exclusion criteria and safety monitoring procedure for the study. **What is an Investigator's Brochure?** The Investigator's Brochure (IB) is a document that details all the clinical and nonclinical data on the investigational medicinal product(s) relevant to a clinical study. The IB provides the investigators and all other personnel involved in the trial with information to aid their understanding of the study design, rationale, dose frequency, administration and safety monitoring procedures. **What is an Investigational Medicinal Product Dossier?** The IMPD provides information related to the quality of the IMP, its manufacture and control, along with data from previous non-clinical and clinical studies, and an overall risk/benefit assessment. The IMPD should also include information on any reference products or any placebos that are intended to be used in a clinical trial. **How do you manage a CTA once it has been approved?** Once a trial has been authorised, there are a number of activities that need to be conducted during the management of the study, as summarised below. **Substantial and Non-Substantial Amendments** During the life-cycle of a clinical trial, a sponsor can change or update data and documents within the original CTA application package approved by the regulatory authorities. Depending on the type of changes proposed, these are classified as either 'substantial' or 'non-substantial' amendments.

SR. NO.	QUESTION ANSWER
	Information on what changes constitute a substantial amendment is available in guidance provided by the European Commission. All substantial amendments must be submitted to the Competent Authorities involved in the study and the Ethics Committee, whereas non-substantial amendments can be made at any time. The following documentation is needed to support an amendment: • amendment form • updated CTA Form and xml file • description of the amendment and justification • copy of the proposed changes • supporting data **Safety Reporting** During the conduct of the trial, it is the responsibility of the sponsor to ensure all Suspected Unexpected Serious Adverse Reactions (SUSARs) are reported to the Competent Authorities. Furthermore, sponsors are required to submit Development Safety Update Reports (DSUR), which take into account all new safety information for the year, along with Investigator's Brochure updates once a year throughout the duration of the clinical trial. **End of Trial Notifications** Upon completion of the trial, a form declaring the end of a clinical trial should be sent to National Competent Authorities within 90 days. **Submission of Study Reports** Upon completion of the trial, the study report should be submitted to the competent authorities within one year of the end of the trial. **WHAT ASSISTANCE CAN S-CUBED PROVIDE?** S-cubed can provide the following EU CTA regulatory support activities: • Prepare, review and finalise the Investigational Medicinal Product Dossier • Prepare and compile the Investigator's Brochure • Prepare and coordinate the preparation of all necessary CTA documents and ensure all documentation is assembled according to the local requirements (from Phase I to IV) • Finalise and submit the CTA • Prepare and submit medical device notifications for non-CE marked devices (as required) • Act as the legal representative for Non-EU sponsors • Support all CTA maintenance activities through to the completion of the study and submission of the End of Trial Notification • Organise meetings with EU regulatory authorities (as required) • Provide ad hoc regulatory and strategic advice to assist the sponsor in managing their EU activities

PHARMA BOOK

SR. NO.	QUESTION ANSWER
	CASE STUDY At S-cubed we have recently assisted a US-based company (with no European presence or regulatory capabilities), with their EU clinical programme. The client required regulatory support for the preparation and compilation of a Clinical Trial Authorisation (CTA) Application for a proposed First-In-Human study. Initially, we provided the client with a comprehensive list of CTA documentation requirements, together with a project plan outlining the timeline for the project deliverables and anticipated CTA approval dates, based on our previous experience of making submissions to the particular regulatory agency. We then conducted a gap analysis of the core supporting data and documents against EU regulatory requirements, and highlighted areas of potential deficiency. Where possible we suggested remedial actions that would address the gaps and support a successful CTA submission. S-cubed was tasked with writing the Investigational Medicinal Product Dossier (IMPD). We ensured that the IMPD, through the inclusion of pharmaceutical development and manufacturing process data, demonstrated that the dosage form, formulation, manufacturing process, device and container closure system were appropriate for the proposed study, and that the products performance was acceptable. We confirmed that the analytical tests outlined in the drug product specification were appropriate and ensured that the release specification acceptance criteria were based both on EU/ICH guidance and ranges seen in previous batch data, and would support the proposed Phase I study. In addition, we conducted a thorough review of the nonclinical data package and provided feedback on safety aspects which might impact the CTA assessment, along with recommendations for future studies. As the study involved the use of a medical device, our team ensured that the study and CTA application satisfied the Medical Devices Regulations governing the use of devices in clinical investigations. We also advised the client on the documentation and importation requirements for other concomitant medications used in the study. We reviewed the clinical protocol and provided input on the trial design, clinical endpoints and inclusion/exclusion criteria, as well as the Investigator's Brochure (IB) and the other CTA documents. As the client was based in the USA, the S-cubed team managed the CTA compilation and submission process on their behalf, and ensured that the local submission requirements were fulfilled. The CTA application submission package was submitted on time (and within budget) and the CTA was approved by the Competent Authority within the clients expected timeline with minimal questions. Our team is now assisting the client with the preparation of an application to obtain a CE-mark for their medical device as well as providing advice for the next phase of their clinical development program.

SR. NO.	QUESTION ANSWER
67.0	**MARKETING AUTHORISATION**
	WHAT IS A MARKETING AUTHORISATION NEEDED FOR? In accordance with EU Directive 2001/83 and Regulation (EC) No. 726/2004 governing medicinal products, in order to legally place a medicinal product on the market in the European Economic Area (EEA), a Marketing Authorisation (MA) or 'licence' must first be approved. To obtain an MA, a Marketing Authorisation Application (MAA) is submitted to the appropriate Competent Authority(s) (CAs), for assessment and MA approval. **WHAT DOES AN MAA CONSIST OF?** An MAA is a comprehensive dossier of information and data describing all aspects (Administrative/Quality/Safety/Efficacy) of a medicinal product demonstrating that it is appropriate for use in patients. There is an internationally agreed standard for the overall content and format for this dossier which is referred to as the Common Technical Document (CTD). The CTD format is applicable for all MAA regulatory submission routes and all product types, although some modifications may be required for certain application/product types. CTD format is also applicable to other submission types including variations and renewals. At the top level, a CTD dossier is split into five modules:
67.1	**Module 1:** Administrative information and prescribing information (any additional region-specific information not specified in the CTD is also included in this module) **Module 2:** CTD Summaries **Module 3:** Quality **Module 4:** Non-clinical Study Reports **Module 5:** Clinical Study Reports The overall organisation of the CTD is fixed and should not be changed. Documents and data should be assigned to the most appropriate sections in Modules 1 to 5. The only exceptions to this are the non-clinical and clinical summaries, within which individual formats/tables can be modified as required to best present the data for assessment. **WHAT INFORMATION AND DATA IS REQUIRED IN EACH CTD MODULE?** Guidance on the top level structure and content of the CTD dossier can be found in Eudralex Volume 2B of EC Notice to Applicants "Presentation and format of the dossier – Common Technical Dossier". CTD does not specify the detailed content in terms of what studies and data are required. There are European Community guidelines regarding the quality, safety and efficacy of medicinal products which

SR. NO.	QUESTION ANSWER
	must be considered and accounted for in preparation of the MAA dossier. In addition, for medicinal product quality, the general chapters and monographs of the European Pharmacopoeia or other national pharmacopoeias should also be accounted for as appropriate. Not all data requirements are mandatory or required for each and every application or product type. If an element is considered to be not relevant or not applicable, the absence of such should be fully justified. There may also be regional differences that will need to be taken into account in dossier preparation. The following is a summarised description of the information to be included in each Module. **Module 1** This Module includes all of the administrative information relating to the application and the concerned medicinal product. Key items for inclusion are: • Cover letter • Application form and annexes (e.g. manufacturing licences, proof of payment of fees, letters of access) • Product Information including the Summary of Product Characteristics (SmPC), labelling, patient leaflet, braille, results of readability testing • Information about the experts • Specific requirements for different types of applications • Environmental Risk Assessment • Pharmacovigilance system description • Risk Management Plan **Module 2** This Module presents summary information for the quality, non-clinical and clinical Modules with so-called expert review of the information and data in the context of the MAA and regulatory framework. **Module 3** Module 3 is the Quality Module which presents all of the information regarding drug substance and drug product development, characterisation, manufacturing and testing to demonstrate that the medicinal product is of suitable quality. **Module 4** This is the Non-clinical Module which includes all of the non-clinical study reports and literature addressing the complete battery of non-clinical testing required for the medicinal product and application type. **Module 5** This is the Clinical Module which includes all of the clinical study reports and literature addressing the clinical requirements for the medicinal product and application type.

SR. NO.	QUESTION ANSWER
	ARE THERE SPECIFIED REQUIREMENTS FOR FORMATTING SUCH AS FILENAMES, MARGINS, FONT TYPE AND SIZE, HYPERLINKING, ETC? There is some general but limited guidance on formatting available, however the aim is obviously to facilitate dossier navigation and review. Margins need to be large enough to ensure that bindings do not obscure any data. The selected font and font size should be easily legible. Times New Roman and 12-point font are recommended for narrative text, although variations to this are accepted, for example for tabulated data where it might be necessary to reduce the font size slightly to ensure a table fits on the page. In terms of pagination and segregation, documentation should be prepared in line with CHMP/ICH/2887/99 Revision 1 Organisation CTD recommendation. National-only submissions must consider any Member State-specific requirements. For example in the UK, the MHRA recommends file naming conventions through Special Mail 5. European submissions would be in accordance with Non-eCTD electronic Submissions (NeeS) or fully electronic (eCTD) format. **IS THERE A REQUIREMENT TO RE-FORMAT OLD DOSSIERS?** There is no obligation to reformat approved dossiers. However it is possible to re-format Quality documentation into Module 3 format in order to facilitate ongoing life-cycle management of the licence, as variations, renewals, etc., will need to be submitted in CTD format. Re-formatting is not recommended for Modules 4 and 5 for Non-clinical and Clinical data. When re-formatting into Module 3, all approved variations must be fully integrated into the re-formatted Module. In terms of the regulatory procedure to be followed to submit the re-formatted Module 3, this does not constitute a variation in itself. Therefore it is recommended that it is submitted as part of another regulatory procedure (e.g. variation or licence renewal), subject to agreement from the concerned CA. If however, an old format licence is to be used as the basis for MAAs to be submitted via the Mutual Recognition Procedure (MRP), the current approved documentation will need to be reformatted into CTD format. It is recommended that Applicants discuss any MRP plans with the proposed Reference Member State (RMS) in advance to determine the best means of doing this, as different Member States may prefer different approaches.

SR. NO.	QUESTION ANSWER
	ARE THERE DIFFERENT NATIONAL ADMINISTRATIVE REQUIREMENTS (I.E. DELIVERY ADDRESSES, NUMBER OF COPIES, PAPER/ELECTRONIC, ETC)? There are likely to be a variety of Member State-specific administrative requirements, some of which are documented in the available EU Guidances. However, there is still the possibility of additional requirements or nuances not readily available in the standard sources of information. In the absence of direct, recent experience of an MAA submission to the concerned Member States (MSs), it is highly recommended that contact be made with the relevant CA to establish any specific national requirements in advance of submission. Requirements for final submission to the MSs again may vary and therefore needs to be checked in advance. In terms of final publication and dispatch of the MAA, this aspect of MAA preparation is often dismissed as minor, yet it requires the same level of care and attention as preparation of the dossier itself. Timelines frequently do not allow much time for this part of the project. Consequently any delays ahead of publication can mean publication and dispatch activities need to be completed at speed, potentially compromising the quality of the final submission. **WHAT ASSISTANCE CAN S-CUBED PROVIDE?** The Regulatory Affairs team at S-cubed has significant experience of MAA preparation submission across the EU. In a recent project, S-cubed assisted the client by: • providing a comprehensive list of country-specific documentation and fees requirements • writing and reviewing the Module 3 Quality section (drug substance and drug product), Modules 2.4 and 2.5 Nonclinical and Clinical Overviews • arranging for experts to review and approve the Overviews • reviewing the clinical- and nonclinical (Modules 4 and 5) MAA sections • compiling the NeeS submission, with creation of bookmarks and hyperlinks • validating the electronic submission with the appropriate Agency checkers • liaising with the RMS and CMSs to ensure the successful validation of the submission • QRD and national templates

SR. NO.	QUESTION ANSWER
	POST-APPROVAL ACTIVITIES S-cubed can provide the following post-approval regulatory support activities: • Licence Renewal Applications through national, mutual recognition, decentralised and centralised procedures • Reclassification Applications • Article 61(3) applications – changes to packaging artwork which do not constitute a variation • Management of sunset clause notifications and requests for waivers • Regulatory compliance reviews checking approved licence information against technical documents used in manufacturing and testing of medicinal products • Change of ownership applications and associated management of changeover of pack artwork and rundown of old stock • Change of Reference Member State (RMS) for licences approved via mutual recognition or decentralised procedures • Assistance with management of site licences (Wholesale dealers and Manufacturers licences) • Review and approval of pack artwork and advertising/promotional materials • All types of Variation Application (please refer to the separate topic "Variations" for more details) • Liaison with Competent Authorities on behalf of Marketing Authorisation Holders (MAHs) • Drug Master File (DMF) reviews

PHARMA BOOK

SR. NO.	QUESTION ANSWER
68.0	**EUDRALEX**
68.1	**TYPES OF VOLUME** **Volume 1 -** EU pharmaceutical legislation for medicinal products for human use **Volume 2 -** Notice to applicants and regulatory guidelines for medicinal products for human use **Volume 3 -** Scientific guidelines for medicinal products for human use **Volume 4 -** Guidelines for good manufacturing practices for medicinal products for human and veterinary use **Volume 5 -** EU pharmaceutical legislation for medicinal products for veterinary use The basic legislation is supported by a series of guidelines that are also published in the following volumes of "The rules governing medicinal products in the European Union": **Volume 6 -** Notice to applicants and regulatory guidelines for medicinal products for veterinary use **Volume 7 -** Scientific guidelines for medicinal products for veterinary use **Volume 8 -** Maximum residue limits **Volume 9 -** Guidelines for pharmacovigilance for medicinal products for human and veterinary use **Volume 10 -** Guidelines for clinical trial. **EudraLex - Volume 4 Good manufacturing practice (GMP) Guidelines.** Volume 4 of "The rules governing medicinal products in the European Union" contains guidance for the interpretation of the principles and guidelines of good manufacturing practices for medicinal products for human and veterinary use laid down in Commission Directives 91/356/EEC, as amended by Directive 2003/94/EC, and 91/412/EEC respectively. **Part I - Basic Requirements for Medicinal Products** **Chapter 1 :** Pharmaceutical Quality System **Chapter 2:** Personnel **Chapter 3 :** Premises and Equipment **Chapter 4 :** Documentation **Chapter 5 :** Production **Chapter 6 :** Quality Control **Chapter 7:** Contract Manufacture and Analysis **Chapter 8 :** Complaints and Product Recall **Chapter 9 :** Self Inspection **Part II - Basic Requirements for Active Substances used as Starting Materials** Basic requirements for active substances used as starting materials

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SR. NO.	QUESTION ANSWER
	Part III - GMP related documents Site Master File Q9 Quality Risk Management Q10 Note for Guidance on Pharmaceutical Quality System MRA Batch Certificate Template for the 'written confirmation' for active substances exported to the European Union for medicinal products for human use **Annex 1** Manufacture of Sterile Medicinal Products **Annex 2** Manufacture of Biological active substances and Medicinal Products for Human Use **Annex 3** Manufacture of Radiopharmaceuticals **Annex 4** Manufacture of Veterinary Medicinal Products other than Immunological Veterinary Medicinal Product **Annex 5** Manufacture of Immunological Veterinary Medicinal Products **Annex 6** Manufacture of Medicinal Gases **Annex 7** Manufacture of Herbal Medicinal Products **Annex 8** Sampling of Starting and Packaging Materials **Annex 9** Manufacture of Liquids, Creams and Ointmentspdf(13 KB) **Annex 10** Manufacture of Pressurised Metered Dose Aerosol Preparations for Inhalation **Annex 11** Computerised Systems (revision January 2011) **Annex 12** Use of Ionising Radiation in the Manufacture of Medicinal Products **Annex 13** Manufacture of Investigational Medicinal Products

SR. NO.	QUESTION ANSWER
	Annex 14 Manufacture of Products derived from Human Blood or Human Plasma **Annex 15** Qualification and validation **Annex 16** Certification by a Qualified person and Batch Release **Annex 17** Parametric Release **Annex 19** Reference and Retention Samples

SR. NO.	QUESTION ANSWER
69.0	**SUPAC**
	The acronym "SUPAC" stands for "Scale-Up and Post-Approval Changes". It refers to the FDA-recommended testing and filing actions to be taken by a pharmaceutical firm when it changes the manufacturing processes of a drug product that has been approved via a New Drug Application (NDA), an Abbreviated New Drug Application (ANDA), or an Abbreviated Antibiotic Drug Application (AADA). The Agency has provided its recommendations to industry in the form of Guidances. As you may be aware, 21 CFR 314.70 already provides instructions for how changes to approved manufacturing process should be reported to the Agency. Specifically, depending on the magnitude of the change and the possibility that the change could negatively affect the product, the Code provides that notification should be accomplished in one of three ways: 1. Via a supplement that requires approval by the FDA prior to implementation of the change; 2. Via a supplement that does not require approval by the FDA prior to implementation of the change ("changes being effected"); 3. Via an annual report.
69.1	Unfortunately, the instructions indicating which type of changes fall into what notification category can be broadly interpreted and are sometimes difficult to follow. Luckily, the regulations [21 CFR 314.70(a)] also indicate that less burdensome routes of notification may be followed if those routes are published in the Federal Register (FR). That is the main purpose of the SUPAC Guidances - to provide industry with clear, streamlined (i.e., "less burdensome") ways to test and report manufacturing changes. (Note: As required by 21 CFR 314.70(a), the documents are issued via the FR.) Why do the SUPAC Guidances offer an advantage over the regulations? • The documents are specific for particular dosage forms. This approach was taken since some product types are more complicated than others, and as such, will likely require more complicated controls. To date, two Guidances have been finalized. They are: Guidance for Industry: Immediate Release Solid Oral Dosage Forms---Scale-Up and Post-Approval Changes: Chemistry, Manufacturing and Controls, In Vitro Dissolution Testing, and In Vivo Bioequivalence Documentation (November 1995) Guidance for Industry: Nonsterile Semisolid Dosage Forms---Scale-Up and Post-Approval Changes: Chemistry, Manufacturing and Controls; In Vitro Dissolution Testing and In Vivo Bioequivalence Documentation (May 1997) In addition, SUPAC documents covering other dosage forms (e.g., extended-release products,

SR. NO.	QUESTION ANSWER
	transdermals, parenteral solutions), as well as a related document(s) for bulk active substances, are at various stages of development. • The FDA and industry have been working very closely to prepare these documents. Industry supplies its input at meetings and workshops as well as through written comments. Although these SUPAC documents are not regulations, the FDA is working to ensure that the Guidances are as consistently interpreted and applied by both the Agency and industry as possible. To this end, the Agency has undertaken a rather comprehensive training program, providing in-house training for its personnel and public workshops for others. Furthermore, although the main thrust of the training is provided at the time a Guidance is issued, the Agency has been diligent in ensuring that subsequent, ongoing interpretation and application of the recommendations remain consistent. In fact, as recent as February 1997, the FDA issued two documents discussing how to properly utilize the SUPAC-IR Guidance for Industry (issued November 1995). These documents are: • Manufacturing Equipment Addendum to the Guidance for Industry for Scale-Up and Post Approval Changes: Immediate Release Products (SUPAC-IR), Draft Guidance for Industry. Released on February 3, 1997. • Letter to industry from Dr. Roger L. Williams, Deputy Center Director for Pharmaceutical Science, CDER, dated February 18, 1997. This letter discussed how industry should interpret stand alone packaging operation site changes and stand alone analytical site changes based upon the Agency's re-assessment of these issues. In addition, it provided the answers to significant questions frequently asked by industry. Finally, you asked how these Guidances affect you and your company, specifically. That depends on what types of products you manufacture, and your job responsibilities in the company. If you are involved in regulatory affairs submission work, scale-up activities, process validation, or analytical testing, you may be affected, assuming your company manufactures immediate release oral dosage forms and nonsterile semisolid dosage forms. (As indicated above, only these two types of products are currently covered by SUPAC Guidances.) If you manufacture another product type, SUPAC won't affect you now; your company must still interpret and follow 21 CFR 314.70. But even if that is the case, keep an eye out for future SUPAC Guidances that could affect your product -- they may be coming soon.

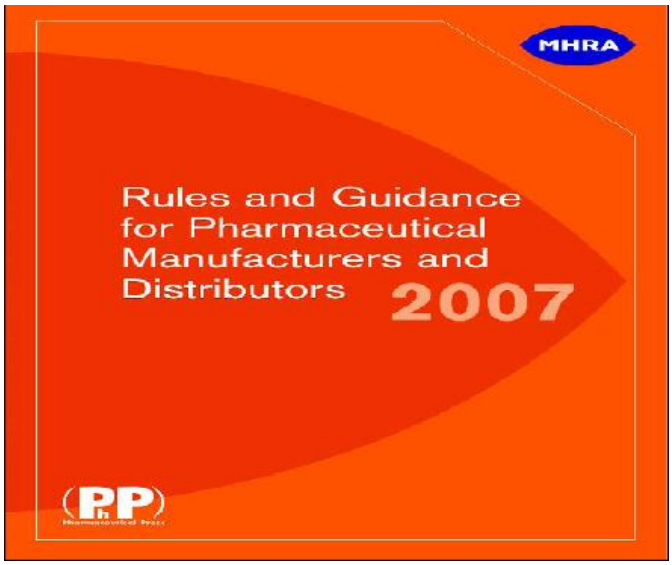
PHARMA BOOK

SR. NO.	QUESTION ANSWER
70.0	**EDQM**
70.1	The European Directorate for the Quality of Medicines & HealthCare (EDQM) is a directorate of the Council of Europe that traces its origins and statutes to an international treaty enabling an international cooperation for the elaboration of a common pharmacopoeia in Europe (Convention on the Elaboration of a European Pharmacopoeia, CETS 50, Council of Europe in 1964,[1] Protocol [2]) In the following you can read on the Certificate of suitability of Monographs of the European Pharmacopoeia (CEP). A manufacturer of a substance can provide proof that the quality of the substance is suitably controlled by the relevant monographs of the European Pharmacopoeia by a CEP granted by the Certification Secretariat of the European Directorate for the Quality of Medicines (EDQM). The CEP confirms that pharmaceutical substances or active pharmaceutical ingredients (API) are produced according to the monographs of the EP. The CEP bridges between European Pharmacopoeia monographs and the need to prepare a file for licensing and thus it also bridges between industry and health authorities.

SR. NO.	QUESTION ANSWER

71.0 ORANGE GUIDELINE (MHRA)

Orange Guideline is a MHRA (U.K) Guideline



71.1

There are 7 sections

- **Section I :** Medicines and Healthcare products Regulatory Agency (MHRA)
- **Section II :** Guidance on Good Manufacturing Practice (GMP)
- **Section III :** Legislation on Manufacture
- **Section IV :** Guidance on Wholesale Distribution Practice
- **Section V :** Legislation on Wholesale Distribution
- **Section VI :** Glossary of Legislation
- **Section VII :** Index

There are 9 Chapters

1. MHRA: Licensing, Inspection and Enforcement for Human Medicines
2. **EU Guidance on Good Manufacturing Practice**
3. UK Guidance on Manufacture
4. EU Legislation on Manufacture
5. UK Legislation on Manufacture
6. EU Guidance on Wholesale Distribution Practice
7. UK Guidance on Wholesale Distribution Practice
8. EU Legislation on Wholesale Distribution
9. UK Legislation on Wholesale Distribution

SR. NO.	QUESTION ANSWER
	There are II Parts in EU Guidance on Good Manufacturing Practice **PART I -** Basic Requirements for Medicinal Products **PART II-** Basic Requirements for Active Substances Used as Starting Materials **In Part I there are 9 contents** 1) Quality Management 2) Personnel 3) Premises and Equipment 4) Documentation 5) Production 6) Quality Control 7) Contract Manufacture and Analysis 8) Complaints and Product Recall 9) Self Inspection

PHARMA BOOK

SR. NO.	QUESTION ANSWER



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