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Good Practices in Production Facilities as Per Various Regulatory Guidelines in Pharmaceutical and Biotech Industry

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ABSTRACT

The factory building(s) for manufacture of drugs shall be so situated and shall have such measures as to avoid risk of contamination from external environment including open sewage, drain, public lavatory or any factory which produce disagreeable or obnoxious odor or fumes, excessive soot, dust, smoke, chemical or biological emissions. Current study is aimed at requirements of Facilities and Equipment as per the different regulatory guidelines viz., WHO, Schedule M of D and C Act, USFDA, MHRA, TGA.

INTRODUCTION

Each of the selected guidelines describes the requirement of Facilities and Equipment under the different chapters as below.

WHO describes the Production in Annexure 3 **WHO good manufacturing practices for pharmaceutical products: Good practices in production**

Schedule M describes the Production in PART **1 Good Manufacturing Practices for Premises and Materials of Good Manufacturing Practices and Requirements of Premises, Plant and Equipment for Pharmaceutical Products - 3. Production area**

USFDA describes the Production in PART 211— Current Good Manufacturing Practice for Finished Pharmaceuticals-CFR Title 21 Chapter I Subchapter C Part 211 Subpart F**— Production and process control**

MHRA describes the Production in **Section II – 2EU Guidance on Good Manufacturing Practice (GMP) - Production**

TGA/PICS describes the Production in **CHAPTER 5 - Production**

Detailed comparison of the selected guidelines with respect to Good practices in production is made in below table:

Table 1: Comparison of regulatory guidelines for Production in pharmaceutical industry

WHO	Schedule M	USFDA	MHRA	TGA/PICS
WHO describes the Production in Annexure 3 **WHO good manufacturing practices for pharmaceutical products: Good practices in production**[1]	**Schedule M** describes the Production in **PART 1 Good Manufacturing Practices For Premises And Materials of**	**USFDA** describes the Production in **PART 211— Current Good Manufacturing Practice for Finished Pharmaceuticals e-CFR Title 21 Chapter**	**MHRA** describes the Production in **Section II – 2EU Guidance On Good Manufacturing Practice (GMP)**	**TGA/PICS** describes the Production in **CHAPTER 5 Production**[5]

WHO	Schedule M	USFDA	MHRA	TGA/PICS
	Good Manufacturing Practices And Requirements of Premises, Plant And Equipment For Pharmaceutical Products[2]	**I Subchapter C** **Part 211 Subpart F** **— Production and process control**[3]	**Production**[4]	
16. Good practices in production **16.1*Principle*** Production operations must follow clearly defined procedures in accordance with manufacturing and marketing authorizations, With the objective of obtaining products of the requisite quality.	**3. Production area:** **3.1.** The production area shall be designed to allow the production preferably in uni-flow and with logical sequence of operations. **3.2.** In order to avoid the risk of cross-contamination, separate	**Production and process control** **211.100 Written procedures; deviations.** (a) There shall be written procedures for production and process control designed to assure that the drug products have the identity, strength, quality, and purity they purport or are represented to possess. Such procedures shall	**5. PRODUCTION** **Principle** Production operations must follow clearly defined procedures; they must comply with the principles of Good Manufacturing Practice in order to obtain products of the requisite	**Chapter 5 PRODUCTION** **Principle** Production operations must follow clearly defined procedures; they must comply with the principles of Good Manufacturing Practice in order to obtain products of the requisite quality

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General **16.2** All handling of materials and products, such as receipt and cleaning, quarantine, sampling, storage, labeling, dispensing, processing, packaging and distribution should be done in accordance with written procedures or instructions and, where necessary, recorded. **16.3** Any deviation from instructions or procedures should be avoided as far as possible. If deviations occur, they should be	dedicated and self-contained facilities shall be made available for the production of sensitive pharmaceutical products like penicillin or biological preparations with live micro-organisms. Separate dedicated facilities shall be provided for the manufacture of contamination causing and potent products such as Beta-Lactum, Sex Hormones and Cytotoxic	include all requirements in this subpart. These written procedures, including any changes, shall be drafted, reviewed, and approved by the appropriate organizational units and reviewed and approved by the quality control unit. (b) Written production and process control procedures shall be followed in the execution of the various production and process control functions and shall be documented at the time of performance. Any deviation from the written procedures shall be recorded	quality and be in accordance with the relevant manufacturing and marketing authorisations. **General** **5.1**Production should be performed and supervised by competent people. **5.2**All handling of materials and products, such as receipt and quarantine, sampling, storage, labeling, dispensing, processing, packaging and	and be in accordance with the relevant manufacturing and marketing authorisations. **GENERAL** **5.1.** Production should be performed and supervised by competent people. **5.2.** All handling of materials and products, such as receipt and quarantine, sampling, storage, labeling, dispensing, processing, packaging and distribution

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done in accordance with an approved procedure. The authorization of the deviation should be approved in writing by a designated person, with the involvement of the QC department, when appropriate. **16.4** Checks on yields and reconciliation of quantities should be carried out as necessary to ensure that there are no discrepancies outside acceptable limits. **16.5** Operations on different products should not be carried out simultaneously or consecutively in the same room or area unless there is	substances. **3.3.** Working and in-process space shall be adequate to permit orderly and logical positioning of equipment and materials and movement of personnel to avoid cross-contamination and to minimize risk of omission or wrong application of any manufacturing and control measures. **3.4.** Pipe-work, electrical fittings, ventilation	and justified. **211.101 Charg-in of components.** Written production and control procedures shall include the following, which are designed to assure that the drug products produced have the identity, strength, quality, and purity they purport or are represented to possess: (a) The batch shall be formulated with the intent to provide not less than 100 percent of the labeled or established amount of active ingredient. (b) Components for drug product manufacturing shall be weighed,	distribution should be done in accordance with written procedures or instructions and, where necessary, recorded. **5.3**All incoming materials should be checked to ensure that the consignment corresponds to the order. Containers should be cleaned where necessary and labeled with the prescribed data. **5.4**Damage to containers and any other problems	should be done in accordance with written procedures or instructions and, where necessary, recorded. **5.3.** All incoming materials should be checked to ensure that the consignment corresponds to the order. Containers should be cleaned where necessary and labeled with the prescribed data. **5.4.** Damage to containers and any other problem which might adversely affect the quality of a

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no risk of mix up or cross-contamination. **16.6** At all times during processing, all materials, bulk containers, major items of equipment, and where appropriate, the rooms and packaging lines being used should be labeled or otherwise identified with an indication of the product or material being processed, its strength (where applicable) and the batch number. Where applicable, this indication should also mention the stage of production. In some cases, it may be useful to also record the name of the previous	openings and similar service lines shall be designed, fixed and constructed to avoid. Service lines shall preferably be identified by colors and the nature of the supply and direction of the flow shall be marked/indicated.	measured, or subdivided as appropriate. If a component is removed from the original container to another, the new container shall be identified with the following information: (1) Component name or item code; (2) Receiving or control number; (3) Weight or measure in new container; (4) Batch for which component was dispensed, including its product name, strength, and lot number. (c) Weighing, measuring, or subdividing operations for	which might adversely affect the quality of a material should be investigated, recorded and reported to the Quality Control Department. **5.5**Incoming materials and finished products should be physically or administratively quarantined immediately after receipt or processing until they have been released for use or distribution. **5.6**Intermediate and bulk products	material should be investigated, recorded and reported to the Quality Control Department. **5.5**. Incoming materials and finished products should be physically or administratively quarantined immediately after receipt or processing until they have been released for use or distribution. **5.6.** Intermediate and bulk products purchased as such should be handled on receipt as though they were starting materials.

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product that has been processed. **16.7** Access to production premises should be restricted to authorized personnel. **16.8** Normally, non-medicinal products should not be produced in areas or with equipment destined for the production of pharmaceutical products. **16.9** In-process controls are usually performed within the production area. The performance of such in-process controls should not have any negative effect on the quality of the product or another product (e.g. cross		components shall be adequately supervised. Each container of component dispensed to manufacturing shall be examined by a second person to assure that: (1) The component was released by the quality control unit; (2) The weight or measure is correct as stated in the batch production records; (3) The containers are properly identified. If the weighing, measuring, or subdividing operations are performed by automated equipment under §211.68, only one	purchased as such should be handled on receipt as though they were starting materials. **5.7**All materials and products should be stored under the appropriate conditions established by the manufacturer and in an orderly fashion to permit batch segregation and stock rotation. **5.8**Checks on yields and reconciliation of quantities should be carried out as necessary to	**5.7.** All materials and products should be stored under the appropriate conditions established by the manufacturer and in an orderly fashion to permit batch segregation and stock rotation. **5.8.** Checks on yields and reconciliation of quantities should be carried out as necessary to ensure that there are no discrepancies outside acceptable limits. **5.9.** Operations on different products should

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contamination or mix up). **Prevention of cross-contamination and bacterial contamination during production** **16.10** When dry materials and products are used in production, special precautions should be taken to prevent the generation and dissemination of dust. Provision should be made for proper air control (e.g. supply and extraction of air of suitable quality). **16.11** Contamination of a starting material or of a product by another material or product must be		person is needed to assure paragraphs (c)(1), (c)(2), and (c)(3) of this section. (d) Each component shall either be added to the batch by one person or verified by a second person or, if the components are added by automated equipment under §211.68, only verified by one person. **211.103 Calculation of yield.** Actual yields and percentages of theoretical yield shall be determined at the conclusion of each appropriate phase of manufacturing, processing,	ensure that there are no discrepancies outside acceptable limits. **5.9** Operations on different products should not be carried out simultaneously or consecutively in the same room unless there is no risk of mix-up or cross-contamination. **5.10** At every stage of processing, products and materials should be protected from microbial and other contamination.	not be carried out simultaneously or consecutively in the same room unless there is no risk of mix-up or cross-contamination. **5.10.** At every stage of processing, products and materials should be protected from microbial and other contamination. **5.11.** When working with dry materials and products, special precautions should be taken to prevent the generation and

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avoided. This risk of accidental cross-contamination arises from the uncontrolled release of dust, gasses, particles, vapors, sprays or organisms from materials and products in process, from residues on equipment, from intruding insects, and from operators' clothing, skin, etc. The significance of this risk varies with the type of contaminant and of the product being contaminated. Among the most hazardous contaminants are highly sensitizing materials, biological preparations such		packaging, or holding of the drug product. Such calculations shall either be performed by one person or independently verified by a second person, or, if the yield is calculated by automated equipment under §211.68, be independently verified by one person. **211.105 Equipment identification.** (a) All compounding and storage containers, processing lines, and major equipment used during the production of a batch of a drug product shall be	**5.11** When working with dry materials and products, special precautions should be taken to prevent the generation and dissemination of dust. This applies particularly to the handling of highly active or sensitizing materials. **5.12** At all times during processing, all materials, bulk containers, major items of equipment and where appropriate rooms used should be labeled or otherwise	dissemination of dust. This applies particularly to the handling of highly active or sensitizing materials. **5.12.** At all times during processing, all materials, bulk containers, major items of equipment and where appropriate rooms used should be labeled or otherwise identified with an indication of the product or material being processed, its strength (where applicable) and batch number. Where applicable, this

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as living organisms, certain hormones, cytotoxic substances, and other highly active materials. Products in which contamination is likely to be most significant are those administered by injection or applied to open wounds and those given in large doses and/or over a long time. **16.12** Cross-contamination should be avoided by taking appropriate technical or organizational measures, for example: (a) carrying out production in dedicated and self-		properly identified at all times to indicate their contents and, when necessary, the phase of processing of the batch. (b) Major equipment shall be identified by a distinctive identification number or code that shall be recorded in the batch production record to show the specific equipment used in the manufacture of each batch of a drug product. In cases where only one of a particular type of equipment exists in a manufacturing facility, the name of the equipment may be used in	identified with an indication of the product or material being processed, its strength (where applicable) and batch number. Where applicable, this indication should also mention the stage of production. **5.13** Labels applied to containers, equipment or premises should be clear, unambiguous and in the company's agreed format. It is often	indication should also mention the stage of production. **5.13.** Labels applied to containers, equipment or premises should be clear, unambiguous and in the company's agreed format. It is often helpful in addition to the wording on the labels to use colors to indicate status (for example, quarantined, accepted, rejected, clean). **5.14.** Checks should be carried out to ensure that

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contained areas (which may be required for products such as penicillins, live vaccines, live bacterial preparations and certain other biologicals); (b) conducting campaign production (separation in time) followed by appropriate cleaning in accordance with a validated cleaning procedure; (c) providing appropriately designed airlocks, pressure differentials, and air supply and extraction systems; (d) minimizing the risk of contamination		lieu of a distinctive identification number or code. **211.110 Sampling and testing of in-process materials and drug products**. (a) To assure batch uniformity and integrity of drug products, written procedures shall be established and followed that describe the in-process controls, and tests or examinations to be conducted on appropriate samples of in-process materials of each batch. Such control procedures shall be established to monitor the output and to validate the performance of	helpful in addition to the wording on the labels to use colors to indicate status (for example, quarantined, accepted, rejected, clean) **5.14** Checks should be carried out to ensure that pipelines and other pieces of equipment used for the transportation of products from one area to another are connected in a correct manner. **5.15** Any deviation from instructions or procedures should be	pipelines and other pieces of equipment used for the transportation of products from one area to another are connected in a correct manner. **5.15.** Any deviation from instructions or procedures should be avoided as far as possible. If a deviation occurs, it should be approved in writing by a competent person, with the involvement of the Quality Control Department when appropriate.

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caused by recirculation or re-entry of untreated or insufficiently treated air; (e) wearing protective clothing where products or materials are handled; (f) using cleaning and decontamination procedures of known effectiveness; (g) using a "closed system" in production; (h) testing for residues; (i) Using cleanliness status labels on equipment. **16.13** Measures to prevent cross-contamination and their effectiveness		those manufacturing processes that may be responsible for causing variability in the characteristics of in-process material and the drug product. Such control procedures shall include, but are not limited to, the following, where appropriate: (1) Tablet or capsule weight variation; (2) Disintegration time; (3) Adequacy of mixing to assure uniformity and homogeneity; (4) Dissolution time and rate; (5) Clarity, completeness, or pH of solutions.	avoided as far as possible. If a deviation occurs, it should be approved in writing by a competent person, with the involvement of the Quality Control Department when appropriate. **5.16** Access to production premises should be restricted to authorized personnel. **5.17** Normally, the production of non-medicinal products should be avoided in	**5.16.** Access to production premises should be restricted to authorized personnel. **5.17.** Normally, the production of non-medicinal products should be avoided in areas and with the equipment destined for the production of medicinal products. **PREVENTION OF CROSS-CONTAMINATION IN PRODUCTION** **5.18.** Contamination of a starting material or of a product by another

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should be checked periodically according to SOPs. **16.14** Production areas where susceptible products are processed should undergo periodic environmental monitoring (e.g. for microbiological monitoring and particulate matter where appropriate). **Processing operations** **16.15** Before any processing operation is started, steps should be taken to ensure that the work area and equipment are clean and free from any starting materials, products, product		(6) Bioburden testing. (b) Valid in-process specifications for such characteristics shall be consistent with drug product final specifications and shall be derived from previous acceptable process average and process variability estimates where possible and determined by the application of suitable statistical procedures where appropriate. Examination and testing of samples shall assure that the drug product and in-process material conform to specifications.	areas and with the equipment destined for the production of medicinal products. **Prevention of Cross-contamination in Production** **5.18** Contamination of a starting material or of a product by another material or product must be avoided. This risk of accidental cross-contamination arises from the uncontrolled release of dust, gasses, vapors, sprays or organisms	material or product must be avoided. This risk of accidental cross-contamination arises from the uncontrolled release of dust, gasses, vapors, sprays or organisms from materials and products in process, from residues on equipment, and from operators' clothing. The significance of this risk varies with the type of contaminant and of product being contaminated. Amongst the most hazardous contaminants are highly

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residues, labels or documents not required for the current operation. **16.16** Any necessary in-process controls and environmental controls should be carried out and recorded. **16.17** Means should be instituted of indicating failures of equipment or of services (e.g. water, gas) to equipment. Defective equipment should be withdrawn from use until the defect has been rectified. After use, production equipment should be cleaned without delay according to detailed written		(c) In-process materials shall be tested for identity, strength, quality, and purity as appropriate, and approved or rejected by the quality control unit, during the production process, e.g., at commencement or completion of significant phases or after storage for long periods. (d) Rejected in-process materials shall be identified and controlled under a quarantine system designed to prevent their use in manufacturing or processing operations for which they are unsuitable. **211.113 Control**	from materials and products in process, from residues on equipment, and from operators' clothing. The significance of this risk varies with the type of contaminant and of product being contaminated. Amongst the most hazardous contaminants are highly sensitizing materials, biological preparations containing living organisms, certain hormones, cytotoxics and other highly	sensitizing materials, biological preparations containing living organisms, certain hormones, cytotoxics, and other highly active materials. Products in which contamination is likely to be most significant are those administered by injection, those given in large doses and/or over a long time. **5.19.** Cross-contamination should be avoided by appropriate technical or

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procedures and stored under clean and dry conditions in a separate area or in a manner that will prevent contamination. **16.18** Time limits for storage of equipment after cleaning and before use should be stated and based on data. **16.19** Containers for filling should be cleaned before filling. Attention should be given to avoiding and removing any contaminants such as glass fragments and metal particles. **16.20** Any significant deviation from the expected yield should be recorded and investigated.		**of microbiological contamination.** (a) Appropriate written procedures, designed to prevent objectionable microorganisms in drug products not required to be sterile, shall be established and followed. (b) Appropriate written procedures, designed to prevent microbiological contamination of drug products purporting to be sterile, shall be established and followed. Such procedures shall include validation of all aseptic and sterilization processes. **211.115 Reproce**	active materials. Products in which contamination is likely to be most significant are those administered by injection, those given in large doses and/or over a long time. **5.19** Cross-contamination should be avoided by appropriate technical or organizational measures, for example: **(a)** production in segregated areas (required for products such as penicillins,	organizational measures, for example: a) production in segregated areas (required for products such as penicillins, live vaccines, live bacterial preparations and some other biologicals), or by campaign (separation in time) followed by appropriate cleaning; b) providing appropriate airlocks and air extraction; c) minimizing the risk of contamination caused by recirculation or re-entry of untreated or

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16.21 Checks should be carried out to ensure that pipelines and other pieces of equipment used for the transportation of products from one area to another are connected in a correct manner. **16.22** Pipes used for conveying distilled or deionized water and, where appropriate, other water pipes should be sanitized and stored according to written procedures that detail the action limits for microbiological contamination and the measures to be taken. **16.23** Measuring, weighing, recording, and		**ssing.** (a) Written procedures shall be established and followed prescribing a system for reprocessing batches that do not conform to standards or specifications and the steps to be taken to insure that the reprocessed batches will conform with all established standards, specifications, and characteristics. (b) Reprocessing shall not be performed without the review and approval of the quality control unit.	live vaccines, live bacterial preparations and some other biologicals), or by campaign (separation in time) followed by appropriate cleaning; **(b)** providing appropriate airlocks and air extraction; **(c)** minimizing the risk of contamination caused by recirculation or re-entry of untreated or insufficiently treated air; **(d)** keeping protective clothing inside areas where products with special risk of cross-	insufficiently treated air; d) keeping protective clothing inside areas where products with special risk of cross-contamination are processed; e) using cleaning and decontaminatio n procedures of known effectiveness, as ineffective cleaning of equipment is a common source of cross-contamination; f) using "closed systems" of production; g) Testing for residues and use of cleaning status labels on

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control equipment and instruments should be serviced and calibrated at prespecified intervals and records maintained. To ensure satisfactory functioning, instruments should be checked daily or prior to use for performing analytical tests. The date of calibration and servicing and the date when recalibration is due should be clearly indicated on a label attached to the instrument. **16.24** Repair and maintenance operations should not present any hazard to the quality of the			contamination are processed; **(e)** using cleaning and decontaminati on procedures of known effectiveness, as ineffective cleaning of equipment is a common source of cross-contamination; **(f)** using "closed systems" of production; **(g)** Testing for residues and use of cleaning status labels on equipment. **5.20** Measures to prevent cross-contamination and their	equipment. **5.20.** Measures to prevent cross-contamination and their effectiveness should be checked periodically according to set procedures. **Validation** **5.21.** Validation studies should reinforce Good Manufacturing Practice and be conducted in accordance with defined procedures. Results and conclusions should be recorded. **5.22.** When any new manufacturing formula or

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products. **Packaging operations** **16.25** When the program for packaging operations is being set up, particular attention should be given to minimizing the risk of cross-contamination, mix-ups or substitutions. Different products should not be packaged in close proximity unless there is physical segregation or an alternative system that will provide equal assurance. **16.26** Before packaging operations are begun, steps should be taken to ensure that the			effectiveness should be checked periodically according to set procedures. **Validation** **5.21** Validation studies should reinforce Good Manufacturing Practice and be conducted in accordance with defined procedures. Results and conclusions should be recorded. **5.22** When any new manufacturing formula or method of preparation is	method of preparation is adopted, steps should be taken to demonstrate its suitability for routine processing. The defined process, using the materials and equipment specified, should be shown to yield a product consistently of the required quality. **5.23.** Significant amendments to the manufacturing process, including any change in equipment or materials, which may affect product

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work area, packaging lines, printing machines and other equipment are clean and free from any products, materials or documents used previously and which are not required for the current operation. The line clearance should be performed according to an appropriate procedure and checklist and recorded. **16.27** The name and batch number of the product being handled should be displayed at each packaging station or line. **16.28** Normally,			adopted, steps should be taken to demonstrate its suitability for routine processing. The defined process, using the materials and equipment specified, should be shown to yield a product consistently of the required quality. **5.23** Significant amendments to the manufacturing process, including any change in equipment or materials, which may affect product quality and/or	quality and/or the reproducibility of the process, should be validated. **5.24.** Processes and procedures should undergo periodic critical revalidation to ensure that they remain capable of achieving the intended results. **Starting Materials** **5.25.** The purchase of starting materials is an important operation which should involve staff who have a particular and thorough knowledge of the suppliers.

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filling and sealing should be followed as quickly as possible by labeling. If labeling is delayed, appropriate procedures should be applied to ensure that no mix ups or mislabelling can occur. **16.29** The correct performance of any printing (e.g. of code numbers or expiry dates) done separately or in the course of the packaging should be checked and recorded. Attention should be paid to printing by hand, which should be rechecked at regular intervals. **16.30** Special care should be taken when cut labels are			the reproducibility of the process should be validated. **5.24** Processes and procedures should undergo periodic critical re-validation to ensure that they remain capable of achieving the intended results. **Starting Materials** **5.25** The purchase of starting materials is an important operation which should involve staff who have a particular and	**5.26.** Starting materials should only be purchased from approved suppliers named in the relevant specification and, where possible, directly from the producer. It is recommended that the specifications established by the manufacturer for the starting materials be discussed with the suppliers. It is of benefit that all aspects of the production and control of the starting material in

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used and when overprinting is carried out off-line, and in hand-packaging operations. Roll feed labels are normally preferable to cut labels in helping to avoid mix ups. Online verification of all labels by automated electronic means can be helpful in preventing mix ups, but checks should be made to ensure that any electronic code readers, label counters, or similar devices are operating correctly. When labels are attached manually, in-process control checks should be performed more frequently.			thorough knowledge of the suppliers. **5.26** Starting materials should only be purchased from approved suppliers named in the relevant specification and, where possible, directly from the producer. It is recommended that the specifications established by the manufacturer for the starting materials be discussed with the suppliers. It is of benefit that all aspects of the production and	question, including handling, labeling and packaging requirements, as well as complaints and rejection procedures, are discussed with the manufacturer and the supplier. **5.27.** For each delivery, the containers should be checked for integrity of package and seal and for correspondence between the delivery note and the supplier's labels. **5.28.** If one

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16.31 Printed and embossed information on packaging materials should be distinct and resistant to fading or erasing. **16.32** Regular online control of the product during packaging should include at least checks on: (a) the general appearance of the packages; (b) whether the packages are complete; (c) whether the correct products and packaging materials are used; (d) whether any overprinting is correct; (e) the correct functioning of line			control of the starting material in question, including handling, labeling and packaging requirements, as well as complaints and rejection procedures, are discussed with the manufacturer and the supplier. **5.27** For each delivery, the containers should be checked for integrity of package and seal and for correspondence between the delivery note and the supplier's	material delivery is made up of different batches, each batch must be considered as separate for sampling, testing and release. **5.29.** Starting materials in the storage area should be appropriately labeled (see Chapter 5, Item 13). Labels should bear at least the following information: □ the designated name of the product and the internal code reference where applicable;

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monitors. Samples taken away from the packaging line should not be returned. 16.33 Products that have been involved in an unusual event during packaging should be reintroduced into the process only after special inspection, investigation and approval by authorized personnel. A detailed record should be kept of this operation. **16.34** Any significant or unusual discrepancy observed during reconciliation of the amount of bulk product and printed			labels. **5.28** If one material delivery is made up of different batches, each batch must be considered as separate for sampling, testing and release. **5.29** Starting materials in the storage area should be appropriately labeled (see Section II, Chapter 5, item 13). Labels should bear at least the following information: _ the designated name of the product and	□ a batch number given at receipt; □ where appropriate, the status of the contents (e.g. in quarantine, on test, released, rejected); □ where appropriate, an expiry date or a date beyond which retesting is necessary. When fully computerized storage systems are used, all the above information should not necessarily be in a legible form on the label. **5.30.** There should be appropriate

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packaging materials and the number of units produced should be investigated, satisfactorily accounted for, and recorded before release. **16.35** Upon completion of a packaging operation, any unused batch-coded packaging materials should be destroyed and the destruction recorded. A documented procedure requiring checks to be performed before returning unused materials should be followed if uncoded printed materials are returned to stock. **16.36** Production			the internal code reference where applicable; _ a batch number given at receipt; _ where appropriate, the status of the contents (e.g. in quarantine, on test, released, rejected); _ where appropriate, an expiry date or a date beyond which retesting is necessary. When fully computerized storage systems are used, all the above	procedures or measures to assure the identity of the contents of each container of starting material. Bulk containers from which samples have been drawn should be identified (see Chapter 6, Item 13). **5.31.** Only starting materials which have been released by the Quality Control Department and which are within their shelf-life should be used. **5.32.** Starting materials should only be dispensed by

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records should be reviewed as part of the approval process of batch release before transfer to the authorized person. Any divergence or failure of a batch to meet production specifications should be thoroughly investigated. The investigation should, if necessary, extend to other batches of the same product and other products that may have been associated with the specific failure or discrepancy. A written record of the investigation should be made and should include the conclusion and follow-up action.			information need not necessarily be in a legible form on the label. **5.30** There should be appropriate procedures or measures to assure the identity of the contents of each container of starting material. Bulk containers from which samples have been drawn should be identified (see Section II, Chapter6, item 13). **5.31** Only starting materials which have	designated persons, following a written procedure, to ensure that the correct materials are accurately weighed or measured into clean and properly labeled containers. **5.33.** Each dispensed material and its weight or volume should be independently checked and the check recorded. **5.34.** Materials dispensed for each batch should be kept together and conspicuously

WHO	Schedule M	USFDA	MHRA	TGA/PICS
			been released by the Quality Control Department and which are within their shelf life should be used. **5.32** Starting materials should only be dispensed by designated persons, following a written procedure, to ensure that the correct materials are accurately weighed or measured into clean and properly labeled containers. **5.33** Each dispensed	labeled as such. **Processing Operations - Intermediate And Bulk Products** **5.35.** Before any processing operation is started, steps should be taken to ensure that the work area and equipment are clean and free from any starting materials, products, product residues or documents not required for the current operation. **5.36.** Intermediate and bulk products should be kept under

WHO	Schedule M	USFDA	MHRA	TGA/PICS
			material and its weight or volume should be independently checked and the check recorded. **5.34** Materials dispensed for each batch should be kept together and conspicuously labeled as such. **Processing Operations: intermediate and bulk products** **5.35** Before any processing operation is started, steps should be taken to ensure that the work area and equipment are	appropriate conditions. **5.37.** Critical processes should be validated (see "VALIDATIO N" in this Chapter). **5.38.** Any necessary in-process controls and environmental controls should be carried out and recorded. **5.39.** Any significant deviation from the expected yield should be recorded and investigated. **Packaging Materials** **5.40.** The purchase, handling and

WHO	Schedule M	USFDA	MHRA	TGA/PICS
			clean and free from any starting materials, products, product residues or documents not required for the current operation. **5.36** Intermediate and bulk products should be kept under appropriate conditions. **5.37** Critical processes should be validated (see "VALIDATION" in this chapter). **5.38** Any necessary in-process controls and	control of primary and printed packaging materials should be accorded attention similar to that given to starting materials. **5.41.** Particular attention should be paid to printed materials. They should be stored in adequately secure conditions such as to exclude unauthorized access. Cut labels and other loose printed materials should be stored and transported in separate closed

WHO	Schedule M	USFDA	MHRA	TGA/PICS
			environmental controls should be carried out and recorded. **5.39** Any significant deviation from the expected yield should be recorded and investigated. **Packaging Materials** **5.40** The purchase, handling and control of primary and printed packaging materials shall be accorded attention similar to that given to starting materials. **5.41** Particular attention	containers so as to avoid mix-ups. Packaging materials should be issued for use only by authorized personnel following an approved and documented procedure. **5.42.** Each delivery or batch of printed or primary packaging material should be given a specific reference number or identification mark. **5.43.** Out-dated or obsolete primary packaging material or

WHO	Schedule M	USFDA	MHRA	TGA/PICS
			should be paid to printed materials. They should be stored inadequately secure conditions such as to exclude unauthorized access. Cut labels and other loose printed materials should be stored and transported in separate closed containers so as to avoid mix-ups. Packaging materials should be issued for use only by authorized personnel following an	printed packaging material should be destroyed and this disposal recorded. **Packaging Operations** **5.44.** When setting up a program for the packaging operations, particular attention should be given to minimizing the risk of cross-contamination, mix-ups or substitutions. Different products should not be packaged in close proximity unless there is physical segregation.

WHO	Schedule M	USFDA	MHRA	TGA/PICS
			approved and documented procedure. **5.42** Each delivery or batch of printed or primary packaging material should be given a specific reference number or identification mark. **5.43** Out-dated or obsolete primary packaging material or printed packaging material should be destroyed and this disposal recorded. **Packaging**	**5.45.** Before packaging operations are begun, steps should be taken to ensure that the work area, packaging lines, printing machines and other equipment are clean and free from any products, materials or documents previously used, if these are not required for the current operation. The line-clearance should be performed according to an appropriate checklist. **5.46.** The name and batch number of the

WHO	Schedule M	USFDA	MHRA	TGA/PICS
			Operations **5.44** When setting up a program for the packaging operations, particular attention should be given to minimizing the risk of cross-contamination, mix-ups or substitutions. Different products should not be packaged in close proximity unless there is physical segregation. **5.45** Before packaging operations are begun, steps should be taken to ensure	product being handled should be displayed at each packaging station or line. **5.47.** All products and packaging materials to be used should be checked on delivery to the packaging department for quantity, identity and conformity with the Packaging Instructions. **5.48.** Containers for filling should be clean before filling. Attention should be given to avoiding and removing any contaminants such as glass

WHO	Schedule M	USFDA	MHRA	TGA/PICS
			that the work area, packaging lines, printing machines and other equipment are clean and free from any products, materials or documents previously used if these are not required for the current operation. The line-clearance should be performed according to an appropriate checklist. **5.46** The name and batch number of the product being handled should be displayed at each	fragments and metal particles. **5.49.** Normally, filling and sealing should be followed as quickly as possible by labeling. If it is not the case, appropriate procedures should be applied to ensure that no mix-ups or mislabelling can occur. **5.50.** The correct performance of any printing operation (for example code numbers, expiry dates) to be done separately or in the course of the packaging

WHO	Schedule M	USFDA	MHRA	TGA/PICS
			packaging station or line. **5.47** All products and packaging materials to be used should be checked on delivery to the packaging department for quantity, identity and conformity with the Packaging Instructions. **5.48** Containers for filling should be clean before filling. Attention should be given to avoiding and removing any contaminants such as glass fragments and	should be checked and recorded. Attention should be paid to printing by hand which should be re-checked at regular intervals. **5.51.** Special care should be taken when using cut-labels and when overprinting is carried out off-line. Roll-feed labels are normally preferable to cut-labels, in helping to avoid mix-ups. **5.52.** Checks should be made to ensure that any electronic code readers,

WHO	Schedule M	USFDA	MHRA	TGA/PICS
			metal particles. **5.49** Normally, filling and sealing should be followed as quickly as possible by labeling. If it is not the case, appropriate procedures should be applied to ensure that no mix-ups or mislabelling can occur. **5.50** The correct performance of any printing operation (for example code numbers, expiry dates) to be done separately or in the course of the packaging	label counters or similar devices are operating correctly. **5.53.** Printed and embossed information on packaging materials should be distinct and resistant to fading or erasing. **5.54.** On-line control of the product during packaging should include at least checking the following: a) general appearance of the packages; b) whether the packages are complete;

WHO	Schedule M	USFDA	MHRA	TGA/PICS
			should be checked and recorded. Attention should be paid to printing by hand which should be re-checked at regular intervals. **5.51** Special care should be taken when using cut labels and when overprinting is carried out off-line. Roll-feed labels are normally preferable to cut labels, in helping to avoid mix-ups. **5.52** Checks should be made to ensure that any	c) whether the correct products and packaging materials are used; d) whether any over-printing is correct; e) correct functioning of line monitors. Samples taken away from the packaging line should not be returned. **5.55.** Products which have been involved in an unusual event should only be reintroduced into the process after special inspection, investigation and approval by authorized personnel.

WHO	Schedule M	USFDA	MHRA	TGA/PICS
			electronic code readers, label counters or similar devices are operating correctly. **5.53** Printed and embossed information on packaging materials should be distinct and resistant to fading or erasing. **5.54** On-line control of the product during packaging should include at least checking the following: **(a)** general appearance of the packages; **(b)** whether the packages	Detailed record should be kept of this operation. **5.56.** Any significant or unusual discrepancy observed during reconciliation of the amount of bulk product and printed packaging materials and the number of units produced should be investigated and satisfactorily accounted for before release. **5.57.** Upon completion of a packaging operation, any unused batch-coded packaging

WHO	Schedule M	USFDA	MHRA	TGA/PICS
			are complete; **(c)** whether the correct products and packaging materials are used; **(d)** whether any over-printing is correct; **(e)** correct functioning of line monitors. Samples taken away from the packaging line should not be returned. **5.55** Products which have been involved in an unusual event should only be reintroduced into the process after special	materials should be destroyed and the destruction recorded. A documented procedure should be followed if uncoded printed materials are returned to stock. **Finished Products** **5.58.** Finished products should be held in quarantine until their final release under conditions established by the manufacturer. **5.59.** The evaluation of finished products and documentation

WHO	Schedule M	USFDA	MHRA	TGA/PICS
			inspection, investigation and approval by authorized personnel. Detailed record should be kept of this operation. **5.56** Any significant or unusual discrepancy observed during reconciliation of the amount of bulk product and printed packaging materials and the number of units produced should be investigated and satisfactorily accounted for before release.	which is necessary before releasing of product for sale are described in Chapter 6 (Quality Control). **5.60.** After release, finished products should be stored as usable stock under conditions established by the manufacturer. **Rejected, recovered and returned materials** **5.61.** Rejected materials and products should be clearly marked as such and stored separately in

WHO	Schedule M	USFDA	MHRA	TGA/PICS
			5.57 Upon completion of a packaging operation, any unused batch-coded packaging materials should be destroyed and the destruction recorded. A documented procedure should be followed if un-coded printed materials are returned to stock. **Finished Products** **5.58** Finished products should be held in quarantine until their final release under conditions established by	restricted areas. They should either be returned to the suppliers or, where appropriate, reprocessed or destroyed. Whatever action is taken should be approved and recorded by authorized personnel. **5.62.** The reprocessing of rejected products should be exceptional. It is only permitted if the quality of the final product is not affected, if the specifications are met and if it is done in accordance

WHO	Schedule M	USFDA	MHRA	TGA/PICS
			the manufacturer. **5.59** The evaluation of finished products and documentation which is necessary before release of product for sale are described in Chapter 6 (Quality Control). **5.60** After release, finished products should be stored as usable stock under conditions established by the manufacturer **Rejected, Recovered**	with a defined and authorized procedure after evaluation of the risks involved. Record should be kept off the reprocessing. **5.63.** The recovery of all or part of earlier batches, which conform to the required quality by incorporation into a batch of the same product at a defined stage of manufacture should be authorized beforehand. This recovery should be carried out in accordance with a defined procedure after

WHO	Schedule M	USFDA	MHRA	TGA/PICS
			and Returned Materials **5.61** Rejected materials and products should be clearly marked as such and stored separately in restricted areas. They should either be returned to the suppliers or, where appropriate, reprocessed or destroyed. Whatever action is taken should be approved and recorded by authorized personnel. **5.62** The reprocessing of rejected products	evaluation of the risks involved, including any possible effect on shelf life. The recovery should be recorded. **5.64.** The need for additional testing of any finished product which has been reprocessed, or into which a recovered product has been incorporated, should be considered by the Quality Control Department. **5.65.** Products returned from the market and which have left

WHO	Schedule M	USFDA	MHRA	TGA/PICS
			should be exceptional. It is only permitted if the quality of the final product is not affected, if the specifications are met and if it is done in accordance with a defined and authorized procedure after evaluation of the risks involved. Record should be kept off the reprocessing. **5.63** The recovery of all or part of earlier batches which conform to the required quality by incorporation into a batch of the same	the control of the manufacturer should be destroyed unless without doubt, their quality is satisfactory; they may be considered for resale, re-labeling or recovery with a subsequent batch only after they have been critically assessed by the Quality Control Department in accordance with a written procedure. The nature of the product, any special storage conditions it requires, its condition and history, and the

WHO	Schedule M	USFDA	MHRA	TGA/PICS
			product at a defined stage of manufacture should be authorized beforehand. This recovery should be carried out in accordance with a defined procedure after evaluation of the risks involved, including any possible effect on shelf life. The recovery should be recorded. **5.64** The need for additional testing of any finished product which has been reprocessed, or into which a recovered product has	time elapsed since it was issued should all be taken into account in this assessment. Where any doubt arises over the quality of the product, it should not be considered suitable for re-issue or re-use, although basic chemical reprocessing to recover active ingredients may be possible. Any action taken should be appropriately recorded.

WHO	Schedule M	USFDA	MHRA	TGA/PICS
			been incorporated, should be considered by the Quality Control Department. **5.65** Products returned from the market and which have left the control of the manufacturer should be destroyed unless without doubt, their quality is satisfactory; they may be considered for resale, re-labelling or recovery in a subsequent batch only after they have been critically assessed by the Quality	

WHO	Schedule M	USFDA	MHRA	TGA/PICS
			Control Department in accordance with a written procedure. The nature of the product, any special storage conditions it requires, its condition and history, and Accepted by venkat the time elapsed since it was issued should all be taken into account in this assessment. Where any doubt arises over the quality of the product, it should not be considered suitable for re-issue or re-use,	

WHO	Schedule M	USFDA	MHRA	TGA/PICS
			although basic chemical reprocessing to recover active ingredient may be possible. Any action taken should be appropriately recorded.	

DISCUSSION

Based on the above comparative study of production controls in the pharmaceutical industry as per WHO, Schedule M of D and C act, USFDA, MHRA and TGA/PICS Good Manufacturing practice guidelines below are the discussion outcomes. Discussion is carried out under different heading for better understanding purpose.

Guidelines Chapters

WHO describes the Production in Annexure 3**WHO good manufacturing practices for pharmaceutical products: Good practices in production**

Schedule M: Schedule M describes the Production in PART **1 Good Manufacturing Practices for Premises and Materials of Good Manufacturing Practices and Requirements of Premises, Plant and Equipment for Pharmaceutical Products**

USFDA: USFDA **describes the Production in** PART 211— Current Good Manufacturing Practice for Finished Pharmaceuticals **e-CFR Title 21Chapter I Subchapter C Part 211 Subpart F— Production and process control**

MHRA: MHRA describes the Production in **Section II – 2EU Guidance on Good Manufacturing Practice (GMP) Production**

TGA/PICS: TGA/PICS describes the Production **in CHAPTER 5Production**

Principle

Production and process controls in pharmaceutical industry work on the principle "Production operations must follow clearly defined procedures; they must comply with the principles of Good Manufacturing Practice in order to obtain products of the requisite quality and be in accordance with the relevant manufacturing and marketing authorizations."

Production Area and Construction features

The production area shall be designed to allow the production preferably in uni-flow and with logical sequence of operations. Pipe-work, electrical fittings, ventilation openings and similar service lines shall be designed, fixed and constructed to avoid. Service lines shall preferably be identified by colors and the nature of the supply and direction of the flow shall be marked/indicated.

WHO describes the nature of construction features for production area in clause 16.22

Schedule M of D and C act describe this requirement under 3.1 and 3.4

Requirement of production area and construction features is not covered under subpart F – Production and process control of USFDA however same is covered under subpart C building and facilities.

MHRA and TGA/PICs describes this requirement under 5.14 however the detailed description for the area and construction features is covered under chapter 3 premises and equipment.

Access to production area

All the selected guidelines details about the access to production area, as per the guidelines, access to production area is restricted and only authorized personnel shall have the access.

WHO describe this requirement under clause 16.7.

Schedule M of D and C act describes this requirement under different chapters of the act.

MHRA and TGA/PICs covered this requirement under 5.16.

USFDA describe this requirement under 211.28 (c) of USFDA, this section is covered under requirement of personnel in pharmaceutical industry.

Written procedures; deviations

All the activities related to production shall be as per the written procedures, requirement of written procedures are described under the different clauses of selected guidelines as follows

WHO describe the requirement of written procedures and deviations under clause 16.2 and 16.3.

Schedule M of Drugs and Cosmetic Act does not detail the requirement of written procedures under the chapter 3. Production area, however, this requirement is detailed under the different chapters of the act.

USFDA describes this requirement under 211.100 written procedures; deviations.

MHRA and TGA/PICs describes the requirement of written procedures under clause 5.2.

Equipment

All the selected guidelines describe the requirement of equipment for production of drug products. The equipment should be installed, qualified and maintained in such a way to fulfill the requirement of product, all the equipment should be cleaned properly to avoid any cross contamination before start of manufacturing activity; same shall be verified and confirmed. The equipment shall be identified properly for its usage, calibration status, content along with date and sign of the personnel identified. If any defective equipment is identified same shall be isolated from the area with proper means or shall be labeled appropriately to avoid usage of such equipment.

Starting and packing materials

The detailed requirement of raw materials or starting materials are given under different chapters of the selected guidelines, however, all the selected guidelines have not described this requirement under production and process control accordingly schedule M of D and C act describe this in chapter 10 Raw materials, WHO guidelines describe this under chapter 14 Materials.

USFDA describe the requirement of starting materials under 211.101 Charge-in of components.

MHRA and TGA/PICs guidelines describe the requirement of starting materials under section starting materials 5.25 to 5.34 and from 5.40 to 5.43 for packing materials.

Weighing and measurement

As per the guidelines selected for study, all the materials used in the production of drug products should be weighed accurately before charging in for production, the measuring, weighing, recording and control equipment and instruments should be serviced and calibrated at prespecified intervals and records of the same shall be maintained. To ensure satisfactory functioning, instruments should be checked daily or prior to use for performing analytical tests. The date of calibration and servicing and the date when recalibration is due should be clearly indicated on a label attached to the instrument.

Prevention of cross contamination

The GMP guidelines selected for study describe the prevention of cross contamination by suitable means. All the guidelines emphasize on the subject under different sections as described below:

WHO describe this under **Prevention of cross-contamination and bacterial contamination during production** from clause 6.10 to 6.14.

Schedule M of D and C act describe this requirement under 3.2.

USFDA guidelines details about the prevention of microbial contamination under 211.113 Control of microbiological contamination.

MHRA and TGA/PICs describe this requirement under Prevention of Cross-contamination in Production 5.18 to 5.20

In-process testing

All the guidelines selected for study describe the requirement of in-process testing to confirm that the product is conforming to predetermined specification.

USFDA describes this requirement under 211.110 Sampling and testing of in-process materials and drug products.

Sampling and testing requirements are not detailed under production in MHRA and TGA guidelines whereas the same is detailed under chapter 6 Quality Control.

WHO describe the same requirement under chapter 17 good practices in quality control.

Schedule M of D and C act describe this under 22.4 testing.

Calculation of yield

Yield calculation is essential to understand the loss during production and to take measures to minimize the loss. Calculation of yield is given under 16.4 of WHO guide, 211.103 of USFDA, 5.8 of MHRA and TGA/ PICs. Schedule M of D and C act describe this requirement under section 12.1 documentation; however schedule M does not specify this requirement under production.

Packing operations

WHO describes the packing operations under 16.25 to 16. 36.

D and C act describe the packing labeling and storage under different category of dosage forms in the act.

MHRA and TGA/PICs describe packing under section **Packaging Operations** 5.44 to 5.57.

USFDA details the packing operations under subpart G packing and labeling control.

RESULTS

Development of Theory for Production and process control in pharmaceutical industry

Based on the above comparative analysis and discussion on production and process control in pharmaceutical industry as per the different regulatory guidelines below is the theory developed which is common for all the regulatory requirement. Following of the below common theory shall suffice the requirements of all the regulatory guidelines with respect to Production and process control.

Production Area

The production area shall be designed to allow the production preferably in uni-flow and with logical sequence of operations.

Pipe-work, electrical fittings, ventilation openings and similar service lines shall be designed, fixed and constructed to avoid cross contaminations. Service lines shall preferably be identified by colors and the nature of the supply and direction of the flow shall be marked/indicated.

Access to production area

Access to production premises should be restricted to authorized personnel.

Written procedure

There shall be written procedures for production and process control designed to assure that the drug products have the identity, strength, quality, and purity they purport or are represented to possess. These written procedures, including any changes, shall be drafted, reviewed, and approved by the appropriate organizational units and reviewed and approved by the quality unit.

Written production and process control procedures shall be followed in the execution of the various production and process control functions and shall be documented at the time of performance. Any deviation from the written procedures shall be recorded and justified.

Equipment

The Equipment used in the production of pharmaceutical products should be of required quality and size. Equipment should not affect the product adversely and it should be designed in such a way that the equipment should be user friendly, safe and cleaning should be easy. Material of construction should not affect the quality of the product.

Normally, non-medicinal products should not be produced in areas or with equipment destined for the production of pharmaceutical products.

Before any processing operation is started, steps should be taken to ensure that the work area and equipment are clean and free from any starting materials, products, product residues, labels or documents not required for the current operation.

All compounding and storage containers, processing lines, and major equipment used during the production of a batch of a drug product shall be properly identified at all times to indicate their contents and, when necessary, the phase of processing of the batch.

Major equipment shall be identified by a distinctive identification number or code that shall be recorded in the batch production record to show the specific equipment used in the manufacture of each batch of a drug product. In cases where only one of a particular type of equipment exists in a manufacturing facility, the name of the equipment may be used in lieu of a distinctive identification number or code.

Starting and packing materials

The purchase of starting materials is an important operation which should involve staff who have a particular and thorough knowledge of the suppliers and manufacturers.

Starting materials should only be purchased from approved supplier named in the relevant specification and, where possible, directly from the producer. It is recommended that the specifications established by the manufacturer for the starting materials be discussed with the Accepted by venkat

suppliers. It is of benefit that all aspects of the production and control of the starting material in question, including handling, labelling and packaging requirements, as well as complaints and rejection procedures, are discussed with the manufacturer and the supplier.

For each delivery, the containers should be checked for integrity of package and seal and for correspondence between the delivery note and the supplier's labels.

If one material delivery is made up of different batches, each batch must be considered as separate for sampling, testing and release.

Starting materials in the storage area should be appropriately labeled. Labels should bear at least the following information:

The designated name of the product and the internal code reference where applicable;

Batch number is given at receipt;

Where appropriate, the status of the contents (e.g. in quarantine, on test, released, rejected);

Where appropriate, an expiry date or a date beyond which retesting is necessary.

There should be appropriate procedures or measures to assure the identity of the contents of each container of starting material. Bulk containers from which samples have been drawn should be identified.

Only starting materials which have been released by the Quality Control Department and which are within their shelf life should be used.

Starting materials should only be dispensed by designated persons, following a written procedure, to ensure that the correct materials are accurately weighed or measured into clean and properly labeled containers.

Each dispensed material and its weight or volume should be independently checked and the check recorded.

Materials dispensed for each batch should be kept together and conspicuously labeled as such.

Packaging Materials

The purchase, handling and control of primary and printed packaging materials shall be accorded attention similar to that given to starting materials.

Particular attention should be paid to printed materials. They should be stored in adequately secure conditions such as to exclude unauthorized access. Cut labels and other loose printed materials should be stored and transported in separate closed containers so as to avoid mix-ups. Packaging materials should be issued for use only by authorized personnel following an approved and documented procedure.

Each delivery or batch of printed or primary packaging material should be given a specific reference number or identification mark.

Out-dated or obsolete primary packaging material or printed packaging material should be destroyed and this disposal recorded.

Weighing and measurement

Measuring, weighing, recording, and control equipment and instruments should be serviced and calibrated at prespecified intervals and records maintained. To ensure satisfactory functioning, instruments should be checked daily or prior to use for performing analytical tests. The date of calibration and servicing and the date when recalibration is due should be clearly indicated on a label attached to the instrument.

Components for drug product manufacturing shall be weighed, measured, or subdivided as appropriate. If a component is removed from the original container to another, the new container shall be identified with the following information:

Component name or item code;

Receiving or control number;

Weight or measure in new container;

Batch for which component was dispensed, including its product name, strength, and lot number.

Weighing, measuring, or subdividing operations for components shall be adequately supervised. Each container of component dispensed to manufacturing shall be examined by a second person to assure that:

The component was released by the quality control unit;

The weight or measure is correct as stated in the batch production records;

The containers are properly identified.

Each component shall either be added to the batch by one person and verified by a second person.

Prevention of cross contamination and Microbial contamination

Appropriate written procedures, designed to prevent objectionable microorganisms in drug products not required to be sterile, shall be established and followed.

Appropriate written procedures, designed to prevent microbiological contamination of drug products purporting to be sterile, shall be established and followed. Such procedures shall include validation of all aseptic and sterilization processes.

When dry materials and products are used in production, special precautions should be taken to prevent the generation and dissemination of dust. Provision should be made for proper air control (e.g. supply and extraction of air of suitable quality).

Contamination of a starting material or of a product by another material or product must be avoided. This risk of accidental cross-contamination arises from the uncontrolled release of dust, gasses, particles, vapors, sprays or organisms from materials and products in process, from residues on equipment, from intruding insects, and from operators' clothing, skin, etc. The significance of this risk varies with the type of contaminant and of the product being contaminated.

Among the most hazardous contaminants are highly sensitizing materials, biological preparations such as living organisms, certain hormones, cytotoxic substances, and other highly active materials.

Products in which contamination is likely to be most significant are those administered by injection or applied to open wounds and those given in large doses and/or over a long time.

Cross-contamination should be avoided by taking appropriate technical or organizational measures, for example:

Carrying out production in dedicated and self-contained areas (which may be required for products such as penicillins, live vaccines, live bacterial preparations and certain other biologicals);

Conducting campaign production (separation in time) followed by appropriate cleaning in accordance with a validated cleaning procedure;

Providing appropriately designed airlocks, pressure differentials, and air supply and extraction systems;

Minimizing the risk of contamination caused by recirculation or re-entry of untreated or insufficiently treated air;

Wearing protective clothing where products or materials are handled;

Using cleaning and decontamination procedures of known effectiveness;

Using a "closed system" in production;

Testing for residues;

Using cleanliness status labels on equipment.

Measures to prevent cross-contamination and their effectiveness should be checked periodically according to SOPs.

Production areas where susceptible products are processed should undergo periodic environmental monitoring (e.g. for microbiological monitoring and particulate matter where appropriate).

Sampling and testing of in-process materials and drug products

To assure batch uniformity and integrity of drug products, written procedures shall be established and followed that describe the in-process controls, and tests or examinations to be conducted on appropriate samples of in-process materials of each batch. Such control procedures shall be established to monitor the output and to validate the performance of those manufacturing processes that may be responsible for causing variability in the characteristics of in-process material and the drug product. Such control procedures shall include, but are not limited to, the following, where appropriate:

Tablet or capsule weight variation;

Disintegration time;

Adequacy of mixing to assure uniformity and homogeneity;

Dissolution time and rate;

Clarity, completeness, or pH of solutions.

Bioburden testing.

Valid in-process specifications for such characteristics shall be consistent with drug product final specifications and shall be derived from previous acceptable process average and process variability estimates where possible and determined by the application of suitable statistical procedures where appropriate. Examination and testing of samples shall assure that the drug product and in-process material conform to specifications.

In-process materials shall be tested for identity, strength, quality, and purity as appropriate, and approved or rejected by the quality control unit, during the production process, e.g., at commencement or completion of significant phases or after storage for long periods.

Rejected in-process materials shall be identified and controlled under a quarantine system designed to prevent their use in manufacturing or processing operations for which they are unsuitable.

Processing operations

Before any processing operation is started, steps should be taken to ensure that the work area and equipment are clean and free from any starting materials, products, product residues, labels or documents not required for the current operation.

Any necessary in-process controls and environmental controls should be carried out and recorded.

Means should be instituted of indicating failures of equipment or of services (e.g. water, gas) to equipment. Defective equipment should be withdrawn from use until the defect has been rectified. After use, production equipment should be cleaned without delay according to detailed written procedures and stored under clean and dry conditions in a separate area or in a manner that will prevent contamination.

Time limits for storage of equipment after cleaning and before use should be stated and based on data.

Containers for filling should be cleaned before filling. Attention should be given to avoiding and removing any contaminants such as glass fragments and metal particles.

Any significant deviation from the expected yield should be recorded and investigated.

Checks should be carried out to ensure that pipelines and other pieces of equipment used for the transportation of products from one area to another are connected in a correct manner.

Pipes used for conveying distilled or deionized water and, where appropriate, other water pipes should be sanitized and stored according to written procedures that detail the action limits for microbiological contamination and the measures to be taken.

Measuring, weighing, recording, and control equipment and instruments should be serviced and calibrated at prespecified intervals and records maintained. To ensure satisfactory functioning, instruments should be checked daily or prior to use for performing analytical tests. The date of calibration and servicing and the date when recalibration is due should be clearly indicated on a label attached to the instrument.

Repair and maintenance operations should not present any hazard to the quality of the products.

Calculation of yield

Actual yields and percentages of theoretical yield shall be determined at the conclusion of each appropriate phase of manufacturing, processing, packaging, or holding of the drug product. Such calculations shall either be performed by one person and independently verified by a second person.

Packing operations

When setting up a program for the packaging operations, particular attention should be given to minimizing the risk of cross-contamination, mix-ups or substitutions. Different products should not be packaged in close proximity unless there is physical segregation.

Before packaging operations are begun, steps should be taken to ensure that the work area, packaging lines, printing machines and other equipment are clean and free from any products, materials or documents previously used, if these are not required for the current operation. The line-clearance should be performed according to an appropriate checklist.

The name and batch number of the product being handled should be displayed at each packaging station or line.

All products and packaging materials to be used should be checked on delivery to the packaging department for quantity, identity and conformity with the Packaging Instructions.

Containers for filling should be clean before filling. Attention should be given to avoiding and removing any contaminants such as glass fragments and metal particles.

Normally, filling and sealing should be followed as quickly as possible by labeling. If it is not the case, appropriate procedures should be applied to ensure that no mix-ups or mislabelling can occur.

The correct performance of any printing operation (for example code numbers, expiry dates) to be done separately or in the course of the packaging should be checked and recorded. Attention should be paid to printing by hand which should be re-checked at regular intervals.

Special care should be taken when using cut labels and when overprinting is carried out off-line. Roll-feed labels are normally preferable to cut labels, in helping to avoid mix-ups.

Checks should be made to ensure that any electronic code readers, label counters or similar devices are operating correctly.

Printed and embossed information on packaging materials should be distinct and resistant to fading or erasing.

On-line control of the product during packaging should include at least checking the following:

General appearance of the packages;

Whether the packages are complete;

Whether the correct products and packaging materials are used;

Whether any over-printing is correct;

Correct functioning of line monitors.

Samples taken away from the packaging line should not be returned.

Products which have been involved in an unusual event should only be reintroduced into the process after special inspection, investigation and approval by authorized personnel. Detailed record should be kept of this operation.

Any significant or unusual discrepancy observed during reconciliation of the amount of bulk product and printed packaging materials and the number of units produced should be investigated and satisfactorily accounted for before release.

Upon completion of a packaging operation, any unused batch-coded packaging materials should be destroyed and the destruction recorded. A documented procedure should be followed if uncoded printed materials are returned to stock.

Finished Products

Finished products should be held in quarantine until their final release under conditions established by the manufacturer.

The evaluation of finished products and documentation which is necessary before releasing of product for sale should be carried out.

After release, finished products should be stored as usable stock under conditions established by the manufacturer.

REFERENCES

1. Annex 3 - WHO good manufacturing practices for pharmaceutical products.
2. PART 1 – Schedule M -Good Manufacturing Practices for Premises and Materials of Good Manufacturing Practices and Requirements of Premises, Plant and Equipment for Pharmaceutical Products.
3. PART 211— USFDA- Current Good Manufacturing Practice for Finished Pharmaceuticals -e-CFR data is current as of January 12, 2016, Title 21 → Chapter I → Subchapter C → Part 211 → Subpart B.
211.100 Written Procedures and deviations.
211.101 Charge in of components
211.103 Calculaton of Yield
211.105 Equipment Identification
211.110 Sampling and testing of in process materials and drug products.
211.113 Control of Microbiological contamination.
211.115 Reprocessing.
4. MHRA -Section II – 2EU Guidance on Good Manufacturing Practice (GMP)-Production.
5. TGA/PICS describes the Production in CHAPTER 5 – Production.