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Good Practices in Quality Control in Pharmaceutical and Biotech Industry an Overview of Various Regulatory Guidelines

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ABSTRACT

Quality Control is concerned with sampling, specifications and testing as well as the organization, documentation and release procedures which ensure that the necessary and relevant tests are carried out and that materials are not released for use, nor products released for sale or supply until their quality has been judged satisfactory. Quality Control is not confined to laboratory operations but must be involved in all decisions which may concern the quality of the product. The independence of Quality Control from Production is considered fundamental to the satisfactory operation of Quality Control.

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INTRODUCTION

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.

Each of the selected guidelines describes the requirement of facilities and equipment under the different chapters as below.

WHO describes the Quality control in Annexure 3**WHO good manufacturing practices for pharmaceutical products: Quality control areas[1].**

USFDA describes the Quality Control in PART 211— Current Good Manufacturing Practice for Finished Pharmaceuticals-CFR data is current as of January 12, 2016 Title 21 → Chapter I → Subchapter C → Part 211 → Subpart I → **Quality control[2].**

Schedule M describes the Quality control 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].**

TGA/PICS describes the Quality Control in **CHAPTER 6 - Quality control[4].**

MHRA describes the Quality Control in **Section II – 2EU Guidance on Good Manufacturing Practice (GMP) Quality control[5].**

Quality Control Department

Based on the comparative study of Quality control in the pharmaceutical industry, we infer that as per WHO, Schedule M of D and C act, and USFDA, MHRA and TGA/PICS guidelines. Discussion is carried out under different heading for better understanding purpose.

Guidelines Chapters

WHO describes the Quality control in Annexure 3 **good manufacturing practices for pharmaceutical products in sec 12.33 to 12.36.**

Schedule M describes the Quality control in PART **1 Good Manufacturing Practices and Requirements of Premises, Plant and Equipment for Pharmaceutical Products in section 5.1 to 5.3.**

USFDA describes the Quality Control in PART 211— Current Good Manufacturing Practice for Finished Pharmaceuticals e-CFR data is latest as of January 12, 2016

Title 21 → Chapter I → Subchapter C → Part 211 → Subpart I → Quality control section 211.160, 165 to 167, 170 and 173

MHRA describes the Quality Control in **Section II 6.1 to 6.30– 2EU Guidance on Good Manufacturing Practice (GMP) Quality control.**

TGA/PICS describe the Quality Control in **CHAPTER 6 section6.1 to 6.30.**

As per WHO, Schedule M, MHRA, TGA and PICS, it is mentioned that separate areas are required for quality control department.

General Requirements:

Quality Control Laboratories shall be independent of the production areas. Separate areas shall be provided each for physicochemical, biological, microbiological or radioisotope analysis. Separate instrument room with adequate area shall be provided for sensitive and sophisticated instruments employed for analysis.

The principle of Quality control department is detailed in WHO, USFDA, MHRA, TGA and PICS which are almost same, and just briefed in Schedule M.

Principle: Quality Control is concerned with sampling, specifications and testing as well as the organization, documentation and release procedures which ensure that the necessary and relevant tests are carried out and that materials are not released for use, nor products released for sale or supply until their quality has been judged satisfactory. Quality Control is not confined to laboratory operations but must be involved in all decisions which may concern

the quality of the product. The independence of Quality Control from Production is considered fundamental to the satisfactory operation of Quality Control.

Quality control Area and Construction features

QC laboratories should be designed to suit the operations to be carried out in them. Sufficient space should be given to avoid mix ups and Cross contamination. There should be adequate suitable storage space for samples, reference standards (if necessary, with cooling), solvents, reagents and records.

The design of the laboratories should take into account the suitability of construction materials, prevention of fumes and ventilation. There should be separate air supply to laboratories and production areas. Separate air handling units and other provisions are needed for biological, Microbiological and radioisotope laboratories.

A separate room may be needed for instruments to protect them against electrical interference, vibration, contact with excessive moisture and other external factors, or where it is necessary to isolate the instruments as inferred by WHO in 12.33 to 12.36.

Schedule M describes this requirement in section 5.2 and 5.3 apart from that it has indicated a separated requirement for sufficient and suitable storage space shall be provided for test samples, retained samples, reference standards, reagents and records.

USFDA and PICS guideline describe the design requirement is very limited in this section.

MHRA/TGA and PICs guideline related to construction describes limited in section 6.1.

1. WHO describes General practices in Quality control in section 17.1:

Quality control is the part of GMP concerned with sampling, specifications and testing, and with the organization and documentation which ensure that the necessary and relevant tests are actually carried out and the materials are not released for use, nor products is released for sale or supply, until their quality has been judged to be satisfactory, QC is not confined to laboratory operations, but may be involved in many decisions concerning the quality of the product.

a) Adequate facilities b) trained personnel c) Approved procedures must be available for sampling, inspecting, and testing starting materials, packaging materials and intermediate,

bulk and finished products and where appropriate for monitoring environmental conditions for GMP purposes. d) All testing shall be carried by approved personnel. e) Qualification and validation for instruments and products. f) Records must be made available with documented evidence and that any deviations have been fully recorded and investigated. g) The finished products are must contain ingredients complying with the qualitative composition of the products described in the marketing authorization; the ingredients must be of the required purity, in their proper container and correctly labeled, same shall be reflected during the analysis in case of any deviations from specified procedures shall be documented and investigated. h) Sufficient samples of starting materials and products (Control samples) must be retained to permit future examination of the product if necessary. i) Quality control shall validate and implement all QC procedures to evaluate, maintain, and store the reference standards for such substances, to ensure correct labeling of containers of materials and products.

2. Schedule M describes in section 5.3 and 5.4 with limited requirements.

3. USFDA General Requirements: Controls on documentation like specification, standard operating procedures, calibration, and reproducibility of test methods, Drug products failing to meet established standards or specifications and any other relevant quality control criteria shall be rejected. Reprocessing may be performed. Prior to acceptance and use, reprocessed material must meet appropriate standards, specifications and any other relevant criteria are described elaborately. i) 211.165 brief about testing and release.

Animals used in the testing components, in-process materials, or drug products for compliance with established specification shall be maintained and controlled for their intended use. Adequate records shall be maintained showing their history of use inferred in section 211.173.

4. European /TGA and PICS guide describe in section 6.1 a) Quality 6.2) principal duties of Quality control describes briefly in chapter 2 of European guideline. 6.3) Finished product describes all relevant factors, including production conditions, results of Raw materials, in process, intermediate tests and finished product testings. And also covered as good quality control laboratory practice in section 6.5 and personnel, premises and equipment in laboratory covered in section 6.6. Whereas sampling procedures are described in section 6.11 to 6.14 and testing procedures described in section 6.15 to 6.32.

Animals used for testing of components materials or products should, where appropriate, be quarantined before use briefed in section 6.22Control of starting materials and intermediate, bulk and finished products. Section 17.6 briefed about the written test procedure for each material or product. In section 17.7 samples should be representative samples. In section 17.8 sampling should be done to avoid cross contamination. In section17.10 sampling equipment should clean and if necessary it is sterilized. In section 17.11 briefed about the labeling part like name of the material, batch number, number of containers, number of samples, and signature of the person and date of sampling. In case of any out of Specification shall be investigated and documented.

Test requirement for starting and packaging materials and batch record review briefed in section 17.13 to 17.19.

In schedule, M is briefed the requirements in 5.1 and 5.2 with limited information.

In case of USFDA is briefed in general requirements 211.160, 211.165, 211.167 and 211.170.

Whereas MHRA/TGA and PICS described in general chapter 6.1 to 6.4. and good quality control laboratory practice.

Batch record review: Batch manufacturing record, batch packaging records, analytical documents, control samples shall be reviewed before release of the batches, in case of any divergence or failure of a batch to meet its specifications should be thorough investigated.

As per Schedule M describes in section 5.2 about the documents with limited information

USFDA described in general requirements section 211.160.

MHRA/TGA and pics guide describes the review of data in documentation section 6.7 to 6.10.

Stability studies: should evaluate the quality and stability of finished pharmaceutical products and when necessary, of starting materials and intermediate products to establish the expiry dates and shelf life of specifications on the basis of stability tests related to storage conditions. A written protocol for ongoing stability determination should be developed.

17.24A Written program for ongoing stability determination should be developed and implemented to include elements such as:

(a) A complete description of the medicine involved in the study

(b) The complete set of testing parameters and methods

c) Provision for sufficient number of Batches

d) Testing schedule

e) Storage condition

f) Sample retention and

g) Summary of the data. IN 17.25 stability shall be determined prior to marketing and following any significant changes in process, equipment, packaging materials etc.,

Tests for potency, purity, and physical characteristics and documented evidence that these tests indicate stability;

In schedule, M of this section is not discussed about the stability studies requirements.

USFDA describes Stability testing in 211.166. There shall be a protocol to assess the characteristics of drug products. The result of such stability studies is useful to identify the storage condition and stability of the product. In this section, it is briefed about the sample size and test intervals, storage conditions, reliable meaningful test methods, testing of drug product in the same pack. Analysis of reconstituted samples or same pack as per the specific procedure. An adequate number of samples and batches and selected time points. Similarly for homeopathic drug products.

Special testing requirements briefed in 211.167 like a) sterile product required like sterility or pyrogen free. b) Ophthalmic ointment to determine the presence of foreign particles or abrasive substance. c) Controlled release dosage to study the rate of release for each active ingredient.

211.170: **Reserve samples** shall be stored for each batch and ingredients at least twice the quantity of samples and shall be retained for 1 year after the expiration date at of the last lot of the drug product contains the active ingredient.

In case of radioactive drug product, except for non-radioactive reagent kits, the reserve sample shall be retained for 3months after the expiration date of the last lot of drug product.

For OTC drug products is exempt for bearing an expiration date, those sample shall be retained for 3 years after distribution of the last lot of drug product.

Reserve samples shall be examined visually at least once a year for evidence of deterioration unless visual examination would affect the integrity of the reserve sample.

In EU guidelines On-going stability program describes In 6.1, 6.2, 6.3 and 6.4 sections. Good quality control laboratory practice.

RESULTS AND DISCUSSION

Development of Theory for Quality control in pharmaceutical and Biotech industry

Based on the above comparative analysis and discussion on Quality control department in pharmaceutical and Biotech 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 Quality control department.

Construction of Quality control department:

Quality Control Laboratories shall be independent of the production areas. Separate areas shall be provided each for physicochemical, biological, microbiological or radioisotope analysis. Separate instrument room with adequate area shall be provided for sensitive and sophisticated instruments employed for analysis. Quality control laboratories should be designed to suit the operations to be carried out in them. Sufficient space should be given to avoid mix ups and Cross contamination. There should be adequate suitable storage space for samples, reference standards (if necessary, with cooling), solvents reagents and records. The design of the lab should take into account the suitability of construction materials, prevention of fumes and ventilation. There should be separate Air supply to laboratories and production areas. Separate Air handling units and other provisions needed for biological, Microbiological and radioisotope laboratories.

A separate room needed for instruments to protect them against electrical interference, vibration contact with excessive moisture and other external factors. A separate room needed for wet analysis to protect them against electrical interference. A separate room needed for Storage of control samples like raw material, packaging material.

(a) The establishment of any specifications, standards, sampling plans, test procedures, or other laboratory control mechanisms required by this subpart, including any change in such specifications, standards, sampling plans, test procedures, or other laboratory control mechanisms, shall be drafted by the appropriate organizational unit and reviewed and approved by the quality control unit. The requirements in this subpart shall be followed and shall be documented at the time of performance. Any deviation from the written specifications, standards, sampling plans, test procedures, or other laboratory control mechanisms shall be recorded and justified.

(b) Laboratory controls shall include the establishment of scientifically sound and appropriate specifications, standards, sampling plans, and test procedures designed to assure that components, drug product containers, closures, in-process materials, labeling, and drug products conform to appropriate standards of identity, strength, quality, and purity. Laboratory controls shall include:

(1) Determination of conformity to applicable written specifications for the acceptance of each lot within each shipment of components, drug product containers, closures, and labeling used in the manufacture, processing, packing, or holding of drug products. The specifications shall include a description of the sampling and testing procedures used. Samples shall be representative and adequately identified. Such procedures shall also require appropriate retesting of any component, drug product container, or closure that is subject to deterioration.

(2) Determination of conformance to written specifications and a description of sampling and testing procedures for in-process materials. Such samples shall be representative and properly identified.

(3) Determination of conformance to written descriptions of sampling procedures and appropriate specifications for drug products. Such samples shall be representative and properly identified.

(4) The calibration of instruments, apparatus, gauges, and recording devices at suitable intervals in accordance with an established written program containing specific directions, schedules, limits for accuracy and precision, and provisions for remedial action in the event.

Accuracy and/or precision limits are not met. Instruments, apparatus, gauges and recording devices not meeting established specifications shall not be used.

211.165 Testing and release for distribution.

(a) For each batch of drug product, there shall be appropriate laboratory determination of satisfactory conformance to final specifications for the drug product, including the identity and strength of each active ingredient, prior to release. Where sterility and/or pyrogen testing are conducted on specific batches of short-lived radiopharmaceuticals, such batches may be released prior to completion of sterility and/or pyrogen testing, provided such testing is completed as soon as possible.

(b) There shall be appropriate laboratory testing, as necessary, of each batch of drug product required to be free of objectionable microorganisms.

(c) Any sampling and testing plans shall be described in written procedures that shall include the method of sampling and the number of units per batch to be tested; such written procedure shall be followed.

(d) Acceptance criteria for the sampling and testing conducted by the quality control unit shall be adequate to assure that batches of drug products meet each appropriate specification and appropriate statistical quality control criteria as a condition for their approval and release. The statistical quality control criteria shall include appropriate acceptance levels and/or appropriate rejection levels.

(e) The accuracy, sensitivity, specificity, and reproducibility of test methods employed by the firm shall be established and documented. Such validation and documentation may be accomplished in accordance with 211.194(a) (2).

(f) Drug products failing to meet established standards or specifications and any other relevant quality control criteria shall be rejected. Reprocessing may be performed. Prior to acceptance and use, reprocessed material must meet appropriate standards, specifications, and any other relevant criteria.

Contract Testing Laboratories.

The personnel, premises, and equipment in the laboratories should be appropriate to the tasks imposed by the nature and the scale of the manufacturing operations. The use of outside laboratories analysis can be accepted based on an evaluation of laboratory control department.

Special testing requirements specific to product requirements

a) Sterile product required like sterility or pyrogen free.

b) Ophthalmic ointment to determine the presence of foreign particles or abrasive substance.

c) Controlled release dosage to study the rate of release of each active ingredient.

Documentation:

An important part of this documentation deals with Quality Control and the following details should be readily available to the Quality Control Department: Specifications; Sampling procedures; Testing procedures and records (including analytical worksheets and/or laboratory notebooks);Analytical reports and/or certificates; Data from environmental monitoring, where required; Validation records of test methods, where applicable; Procedures for and records of the calibration of instruments and maintenance of equipment.

Any Quality Control documentation relating to a batch record should be retained for one year after the expiry date of the batch and at least 5 years after the certification referred to in Article 51(3) of Directive 2001/83/EC.

For some kinds of data (e.g. analytical tests results, yields, and environmental controls) it is recommended that records are kept in a manner permitting trend evaluation. In addition to the information which is part of the batch record, other original data such as laboratory notebooks and/or records should be retained and readily available.

On-going stability program:

After marketing, the stability of the medicinal product should be monitored according to a continuous appropriate program that will permit the detection of any stability issue (e.g. changes in levels of impurities or dissolution profile) associated with the formulation in the marketed package. The purpose of the on-going stability program is to monitor the product over its shelf life and to determine that the product remains, and can be expected to remain, within specifications under the labeled storage conditions. This mainly applies to the medicinal product in the package in which it is sold, but consideration should also be given to the inclusion in the program of bulk product. For example, when the bulk product is stored for a long period before being packaged and/or shipped from a manufacturing site to a

packaging site, the impact on the stability of the packaged product should be evaluated and studied under ambient conditions. In addition, consideration should be given to intermediates that are stored and used over prolonged periods. Stability studies on reconstituted product are performed during product development and need not be monitored on an on-going basis. However, when relevant, the stability of reconstituted product can also be monitored.

The on-going stability program should be described in a written protocol following the general rules of Chapter 4 and results formalized as a report. The equipment used for the on-going stability program (stability chambers among others) should be qualified and maintained following the general rules of Chapter 3 - Annex 15 as per EU guideline.

The protocol for an on-going stability programme should extend to the end of the shelf life period and should include, but not be limited to, the following parameters: Number of batch(es) per strength and different batch sizes, if applicable; relevant physical, chemical, microbiological and biological test methods; acceptance criteria; reference to test methods; description of the container closure system(s);testing intervals (time points); description of the conditions of storage (standardized ICH conditions for long-term testing, consistent with the product labeling, should be used); other applicable parameters specific to the medicinal product. The protocol for the on-going stability program can be different from that of the initial long-term stability study as submitted in the marketing authorization dossier provided that this is justified and documented in the protocol (for example the frequency of testing, or when updating to ICH recommendations).The number of batches and frequency of testing should provide a sufficient amount of data to allow for trend analysis. Unless otherwise justified, at least one batch per year of product manufactured in every strength and every primary packaging type, if relevant, should be included in the stability program (unless none are produced during that year). For products where on-going stability monitoring would normally require testing using animals and no appropriate alternative, validated techniques are available, the frequency of testing may take account of a risk-benefit approach. The principle of bracketing and matrix designs may be applied if scientifically justified in the protocol.

In certain situations, additional batches should be included in the on-going stability program. For example, an on-going stability study should be conducted after any significant change or significant deviation to the process or package. Any reworking, reprocessing or recovery operation should also be considered for inclusion.

Results of on-going stability studies should be made available to key Personnel and, in particular, to the Qualified Person(s). Where on-going stability studies are carried out at a site other than the site of manufacture of the bulk or finished product, there should be a written agreement between the parties concerned. Results of on-going stability studies should be available at the site of manufacture for review by the competent authority.

Out of specification or significant atypical trends should be investigated. Any confirmed out of specification result, or significant negative trend, should be reported to the relevant competent authorities. The possible impact on batches on the market should be considered in accordance with Chapter 8 of EU GMP Guide and in consultation with the relevant competent authorities.

A summary of all the data generated, including any interim conclusions on the program, should be written and maintained. This summary should be subjected to periodic review.

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