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## Quality Assurance and Self - Inspection in Pharmaceutical Industry with EU Variation

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### ABSTRACT

As per the comparative evaluation of different regulatory guidelines with respect to Quality Risk Management, It is found that Quality Risk Management is not covered in all the selected guidelines, WHO GMP guide is having the information on QRM procedure and other selected guidelines is not having the information on QRM procedure, however it is cross-referenced to ICH Q9 in USFDA guideline. However, implementing the QRM procedure in the pharmaceutical industry will suffice the requirement of all the guidelines. The purpose of self-inspection is to evaluate the manufacturer's compliance with GMP in all aspects of production and QC. The self-inspection programme should be designed to detect any shortcomings in the implementation of GMP and to recommend the necessary corrective actions. Self-inspections should be performed routinely, and maybe, in addition, performed on special occasions, e.g. in the case of product recalls or repeated rejections, or when an inspection by the health authorities is announced. The team responsible for self-inspection should consist of personnel who can evaluate the implementation of GMP objectively.



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## INTRODUCTION

### **Development of Theory for Quality Assurance requirement in the pharmaceutical industry**

Quality Assurance in the pharmaceutical industry as per the different regulatory guidelines below is the theory developed which is common for the entire regulatory requirement. Following the below common theory shall suffice the requirements of all the regulatory guidelines with respect to Quality Assurance.

#### **Responsibilities of QA:**

As per the above comparative evaluation of different regulatory guidelines with respect to Responsibilities of Quality Assurance, below are the duties to be carried out by QA and are to be specifically documented in the job description to suffice the requirement of all selected regulatory guidelines.

- (a) Pharmaceutical products are designed and developed in a way that takes account of the requirements of GMP and other associated codes such as those of good laboratory practice and good clinical practice;
- (b) Production and control operations are clearly specified in a written form and GMP requirements are adopted;
- (c) Managerial responsibilities are clearly specified in job descriptions;
- (d) Arrangements are made for the manufacture, supply, and use of the correct starting and packaging materials;
- (e) All necessary controls on starting materials, intermediate products, and bulk products and other in-process controls, calibrations, and validations are carried out;
- (f) The finished product is correctly processed and checked, according to the defined procedures;
- (g) Pharmaceutical products are not sold or supplied before the authorized persons have certified that each production batch has been produced and controlled in accordance with the

requirements of the marketing authorization and any other regulations relevant to the production, control, and release of pharmaceutical products;

(h) SATISFACTORY arrangements exist to ensure, as far as possible, that the pharmaceutical products are stored by the manufacturer, distributor, and subsequently handled so that quality is maintained throughout their shelf-life;

(i) There is a procedure for self-inspection and/or quality audit that regularly appraises the effectiveness and applicability of the QA system;

(j) Deviations are reported, investigated and recorded;

(k) There is a system for approving changes that may have an impact on product quality;

(l) Regular evaluations of the quality of pharmaceutical products should be conducted with the objective of verifying the consistency of the process and ensuring its continuous improvement; and

(m) There is a system for QRM.

#### **Quality risk management:**

As per the above comparative evaluation of different regulatory guidelines with respect to Quality Risk Management, It is found that Quality Risk Management is not covered in all the selected guidelines, WHO GMP guide is having the information on QRM procedure and other selected guidelines is not having the information on QRM procedure, however it is cross-referenced to ICH Q9 in USFDA guideline. However, implementing the QRM procedure in the pharmaceutical industry will suffice the requirement of all the guidelines.

#### **Annual Product Quality Review:**

Annual Product Quality Review is mentioned in WHO GMP guide, USFDA Guide, MHRA Guide, TGA/ PICs guide but it is not specified in Schedule M of Drugs and Cosmetics Act. Conducting and recording Annual Product Quality Review in the pharmaceutical industry will suffice the requirements of all the regulatory guidelines.

## **SELF - INSPECTION IN PHARMACEUTICAL INDUSTRY**

The purpose of self-inspection is to evaluate the manufacturer's compliance with GMP in all aspects of production and QC. The self-inspection programme should be designed to detect any shortcomings in the implementation of GMP and to recommend the necessary corrective actions. Self-inspections should be performed routinely, and maybe, in addition, performed on special occasions, e.g. in the case of product recalls or repeated rejections, or when an inspection by the health authorities is announced. The team responsible for self-inspection should consist of personnel who can evaluate the implementation of GMP objectively. All recommendations for corrective action should be implemented. The procedure for self-inspection should be documented, and there should be an effective follow-up programme.

A current study is aimed at requirements of self- inspection 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 self-inspection under the different chapters as below.

**WHO** describes the Self-inspection in Annexure 3 **WHO good manufacturing practices for pharmaceutical products: Good practices in Self-inspection, quality audits and supplier's audits, and approval**

**Schedule M** describes the Self-inspection in **PART 1 Good Manufacturing Practices for Premises and Materials of Good Manufacturing Practices and Requirements of Premises, Plant And Equipment for Pharmaceutical Products - 15. Self-Inspection and Quality audit:-**

USFDA describes the Self Inspection in PART 211— 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 → — **Self Inspection**

### **D. Evaluation of Activities2. Conduct Internal Audits**

**MHRA** describes the Self Inspection in **Section II – 2EU Guidance On Good Manufacturing Practice (GMP) - Self-Inspection**

**TGA/PICS** describes the Self Inspection in **CHAPTER 9Quality Management Self-Inspection** 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 Self-Inspection in the pharmaceutical industry**

WHO	Schedule M	USFDA	MHRA	TGA/PICS
<p><b>WHO</b> describes the Self-inspection in Annexure 3</p> <p><b>WHO good manufacturing practices for pharmaceutical products: Good practices in Self-inspection</b></p>	<p><b>Schedule M</b> describes the Self-inspection in <b>PART 1 Good Manufacturing Practices For Premises And Materials of Good Manufacturing Practices And Requirements Of Premises, Plant And Equipment For Pharmaceutical Products</b></p>	<p><b>USFDA describes the Self Inspection in PART 211—Current Good Manufacturing Practice for Finished Pharmaceuticals</b></p> <p>e-CFR data is current as of <b>January 12, 2016</b></p> <p><u>Title</u>  <u>21</u> → <u>Chapter I</u> → <u>Subchapter C</u> → <u>Part 211</u> → <u>Subpart B</u> → <b>Self Inspection</b></p>	<p><b>MHRA</b> describes the Self Inspection in <b>Section II – 2EU Guidance On Good Manufacturing Practice (GMP) - Self-Inspection</b></p>	<p><b>TGA/PICS</b> describes the Self Inspection in <b>CHAPTER 9 Quality Management - Self-Inspection</b></p>
<p><b>Self-inspection, quality audits and supplier’s audits and approval</b></p> <p><b>8.1 Principle.</b> The purpose of self-inspection is to evaluate the manufacturer’s compliance with GMP in all aspects of production and QC. The self-inspection programme should be designed to detect any</p>	<p><b>15. Self-Inspection and Quality audit:–</b> It may be useful to constitute a self-inspection team supplemented with a quality audit procedure for assessment of all or part of a system with the specific purpose of improving it.</p> <p><b>15.1</b> To evaluate the manufacturer's compliance with GMP in all aspects of</p>	<p><b>D. Evaluation Activities</b></p> <p><b>2. Conduct Internal Audits</b></p> <p>A quality systems approach calls for audits to be conducted at planned intervals to evaluate effective implementation and maintenance of the quality system and to determine if processes and products meet established parameters and</p>	<p><b>Principle</b> Self-inspections should be conducted in order to monitor the implementation and compliance with Good Manufacturing Practice principles and to propose necessary corrective measures.</p> <p><b>9.1</b> Personnel matters, premises, equipment,</p>	<p><b>Principle</b> Self-inspections should be conducted in order to monitor the implementation and compliance with Good Manufacturing Practice principles and to propose necessary corrective measures.</p> <p><b>9.1.</b> Personnel matters, premises,</p>

WHO	Schedule M	USFDA	MHRA	TGA/PICS
<p>shortcomings in the implementation of GMP and to recommend the necessary corrective actions. Self-inspections should be performed routinely, and maybe, in addition, performed on special occasions, e.g. in the case of product recalls or repeated rejections, or when an inspection by the health authorities is announced. The team responsible for self-inspection should consist of personnel who can evaluate the implementation of GMP objectively. All recommendations for corrective action should be implemented. The procedure for self-inspection should be documented, and there should be an effective follow-up programme.</p> <p><b>Items for self-</b></p>	<p>production and quality control, the concept of self-inspection shall be followed. The manufacturer shall constitute a team of independent, experienced, qualified persons from within or outside the company, who can audit objectively the implementation of methodology and procedures evolved. The procedure for self-inspection shall be documented indicating self-inspection results, evaluation, conclusions and recommended corrective actions with an effective follow-up program. The recommendations for corrective action shall be adopted.</p> <p><b>15.2</b> The program shall be designed to detect shortcomings in the implementation of Good Manufacturing</p>	<p>specifications. As with other procedures, audit procedures should be developed and documented to ensure that the planned audit schedule takes into account the relative risks of the various quality system activities, the results of previous audits and corrective actions, and the need to audit the complete system. Procedures should describe how auditors are trained in objective evidence gathering, their responsibilities, and auditing procedures. Procedures should also define auditing activities such as the scope and methodology of the audit, selection of auditors, and audit conduct (audit plans, opening meetings, interviews, closing meeting, and reports). It is critical to</p>	<p>documentation, production, quality control, distribution of the medicinal products, arrangements for dealing with complaints and recalls, and self-inspection, should be examined at intervals following a pre-arranged programme in order to verify their conformity with the principles of Quality Assurance.</p> <p><b>9.2</b> Self-inspections should be conducted in an independent and detailed way by a designated competent person(s) from the company. Independent audits by external experts may also be useful.</p> <p><b>9.3</b> All self-inspections should be recorded. Reports should contain all the observations</p>	<p>equipment, documentation, production, quality control, distribution of the medicinal products, arrangements for dealing with complaints and recalls, and self-inspection, should be examined at intervals following a pre-arranged programme in order to verify their conformity with the principles of Quality Assurance.</p> <p><b>9.2.</b> Self-inspections should be conducted in an independent and detailed way by a designated competent person(s) from the company. Independent audits by external experts may also be useful.</p> <p><b>9.3.</b> All self-inspections should be recorded. Reports should contain all the</p>

WHO	Schedule M	USFDA	MHRA	TGA/PICS
<p><b>inspection</b></p> <p><b>8.2</b> Written instructions for self-inspection should be established to provide a minimum and uniform standard of requirements. These may include questionnaires on GMP requirements covering at least the following items:</p> <p>(a) personnel;</p> <p>(b) premises including personnel facilities;</p> <p>(c) maintenance of buildings and equipment;</p> <p>(d) storage of starting materials and finished products;</p> <p>(e) equipment;</p> <p>(f) production and in-process controls;</p> <p>(g) QC;</p> <p>(h) documentation;</p> <p>(i) sanitation and hygiene;</p> <p>(j) validation and revalidation programmers;</p> <p>(k) calibration of instruments or measurement systems;</p> <p>(l) recall procedures;</p>	<p>Practice and to recommend the necessary corrective actions. Self-inspections shall be performed routinely and on specific occasions, like when product recalls or repeated rejections occur or when an inspection by the licensing authorities is announced. The team responsible for self-inspection shall consist of personnel who can evaluate the implementation of Good Manufacturing Practice objectively; all recommendations for corrective action shall be implemented.</p> <p><b>15.3</b> Written instructions for self-inspection shall be drawn up which shall include the following: -</p> <p>(a) Personnel.</p> <p>(b) Premises including personnel facilities.</p> <p>(c) Maintenance of buildings and</p>	<p>maintain records of audit findings and assign responsibility for follow-up to prevent problems from recurring</p>	<p>made during the inspections and, where applicable, proposals for corrective measures. Statements on the actions subsequently taken should also be recorded.</p> <p><b>2.4 Internal Audits (Self Inspection)</b></p> <p><b>2.40</b> In order to verify compliance with the principles of GMP for APIs, regular internal audits should be performed in accordance with an approved schedule.</p> <p><b>2.41</b> Audit findings and corrective actions should be documented and brought to the attention of responsible management of the firm. Agreed corrective actions should be completed in a timely and effective manner.</p>	<p>observations made during the inspections and, where applicable, proposals for corrective measures. Statements on the actions subsequently taken should also be recorded.</p>



WHO	Schedule M	USFDA	MHRA	TGA/PICS
<p>(m) complaints management;</p> <p>(n) labels control;</p> <p>(o) Results of previous self-inspections and any corrective steps are taken.</p> <p><b>Self-inspection team</b></p> <p><b>8.3</b> Management should appoint a self-inspection team consisting of experts in their respective fields and familiar with GMP. The members of the team may be appointed from inside or outside the company.</p> <p><b>Frequency of self-inspection</b></p> <p><b>8.4</b> The frequency at which self-inspections are conducted may depend on company requirements but should preferably once in a year</p>	<p>equipment</p> <p>(d) Storage of starting materials and finished products.</p> <p>(e) Equipment.</p> <p>(f) Production and in-process controls.</p> <p>(g) Quality control.</p> <p>(h) Documentation.</p> <p>(i) Sanitation and hygiene.</p> <p>(j) Validation and revalidation programmes.</p> <p>(k) Calibration of instruments or measurement systems.</p> <p>(l) Recall procedures.</p> <p>(m) Complaints management.</p> <p>(n) Labels control.</p> <p>(o) Results of previous self-inspections and any corrective steps are taken.</p>			

## EU (Variation)<sup>102</sup>

All changes subsequent to their placing on the EU market, e.g. changes to the production process, product packaging or the address of the manufacturer, are considered in legal terms as 'variations', and must be handled in accordance with a complex legislative framework: the 'Variations Regulation.

### Variation categories are defined as

1. **Minor variation type IA:** variation which has only a minimal or no impact, on the quality, safety or efficacy of the product
2. **Major variation type II:** variation which is not a line extension, but may have a significant impact on the quality, safety or efficacy of the medicinal product
3. **Minor variation type IB:** variation which is neither a minor type IA nor a major type II nor an extension
4. **Extension of a marketing authorization:** a variation which is listed in Annex I and fulfills the conditions therein

### 1. Following Variations are classified as minor variations of type IA

- a. Variations of purely administrative nature that are related to the identity and contact details of:— the holder;  
— the manufacturer or supplier of any starting material, reagent, intermediate, active substance used in the manufacturing process or finished product;
- b. variations related to the deletion of any manufacturing site, including for an active substance, intermediate or finished product, packaging site, manufacturer responsible for the batch release, a site where batch control takes place;
- c. variations related to minor changes to an approved physicochemical test procedure, where the updated procedure is demonstrated to be at least equivalent to the former test procedure, appropriate validation studies have been performed and the results show that the updated test procedure is at least equivalent to the former;

- d. variations related to changes made to the specifications of the active substance or of an excipient in order to comply with an update of the relevant monograph of the European Pharmacopoeia or of the national pharmacopoeia of a Member State, where the change is made exclusively to comply with the pharmacopoeia and the specifications for product-specific properties are unchanged;
- e. Variations related to changes in the packaging material not in contact with the finished product, which does not affect the delivery, use, safety or stability of the medicinal product;
- f. Variations related to the tightening of specification limits, where the change is not a consequence of any commitment from previous assessment to review specification limits and does not result from unexpected events arising during manufacture.

#### **Timelines for national variations – Type IA**

- Type IA not requiring immediate notification – up to 12 months following the implementation and can be submitted as one report including all the variations together.
- Type IA<sub>IN</sub> requires submission immediately after the implementation – important for the continuous supervision of the medicinal product concerned.
- Within 30 days following receipt of the notification, the RMS will inform finally if the decision is accepted or rejected.

#### **Timelines for national variations – Type IB**

- Simultaneous submission to all relevant authorities a notification containing the elements listed in Annex IV<sup>113</sup>. If the notification fulfills the requirements the RMS shall, after consulting the other Member States concerned (CMS), acknowledge receipt of a valid notification.
- If within 30 days of acknowledgment, no unfavorable opinion is received, the notification is considered acceptable. The RMS will inform finally if the decision is accepted or rejected.

## **2. Following Variations are classified as major variations of type II**

- a. variations related to the addition of a new therapeutic indication or to the modification of an existing one;

- b. variations related to significant modifications of the summary of product characteristics due in particular to new quality, pre-clinical, clinical or Pharmacovigilance findings;
- c. variations related to changes outside the range of approved specifications, limits or acceptance criteria;
- d. variations related to substantial changes to the manufacturing process, formulation, specifications or impurity profile of the active substance or finished medicinal product which may have a significant impact on the quality, safety or efficacy of the medicinal product;
- e. variations related to modifications in the manufacturing process or sites of the active substance for a biological medicinal product;
- f. Variations related to the introduction of a new design space or the extension of an approved one, where the design space has been developed in accordance with the relevant European and international scientific guidelines.

### **Timelines for national variations – Type II**

- Simultaneous submission to all relevant authorities an application containing the elements listed in Annex IV. If the application fulfills the requirements the RMS will acknowledge receipt of a valid application, the procedure will start from this acknowledgment date.
- Within 60 days the RMS will prepare an assessment report and a decision on the application, which shall be communicated to the CMS. If urgent the period may be shortened, or extended to 90 days for variations listed in Part 1 of Annex V.
- Within 30 days following receipt of the decision and the RMS assessment, the CMS will recognize the decision and inform RMS. No disagreement from the CMS will be considered as recognition of the decision. The RMS will inform finally if the decision is accepted or rejected.

### **3. Extension applications**

Extension of a marketing authorization' or 'extension' means a variation which is listed in Annex I.

It lists 3 main categories

- A. Changes to the active substance(s)
- B. Changes to strength, pharmaceutical form, and route of administration.
- C. Other changes specific to veterinary medicinal products to be administered to food-producing animals



**Table 2: Extension Application**

<b>A.</b>	<b>Changes to the active substance(s)</b>
(i)	Replacement of the active substance(s) by a different salt/ester complex/derivative (with the same therapeutic moiety) where the efficacy/safety characteristics are not significantly different
(ii)	Replacement by a different isomer, a different mixture of isomers, of a mixture by an isolated isomer (e.g. racemate by a single enantiomer) where the efficacy/safety characteristics are not significantly different
(iii)	Replacement of a biological substance or product of biotechnology with one of a slightly different molecular structure. Modification of the vector used to produce the antigen/source material, including a new master cell bank from a different source where the efficacy/safety characteristics are not significantly different
(iv)	A new ligand or coupling mechanism for a radiopharmaceutical
(v)	Change to the extraction solvent or the ratio of herbal drug to herbal drug preparation where the efficacy/safety characteristics are not significantly different
<b>B.</b>	<b>Change to strength, pharmaceutical form, route of administration</b>
(i)	Change of bioavailability
(ii)	Change of pharmacokinetics e.g. change in the rate of release
(iii)	Change or addition of a new strength/potency
(iv)	Change or addition of a new pharmaceutical form
(v)	Change or addition of a new route of administration
<b>C.</b>	<b>Other changes specific to veterinary medicinal products to be administered to food-producing animals: change or addition of target species.</b>

**Table 3: Comparison of generic drug dossier requirement for the US and Europe**

Item	USA	EU
Criteria for generic drugs	<p>Approval as a generic drug when</p> <ul style="list-style-type: none"> <li>Contain the same active ingredient as the innovator drug, i.e. the same salt and ester of the same therapeutic moiety. Inactive ingredients may vary.</li> <li>be identical in strength, dosage form, and route of administration</li> <li>have the same use indications</li> <li>be bioequivalent to the originator product</li> <li>meet the same batch requirements for identity, strength,</li> </ul>	<p>Claiming essential similarity to an original/reference product, when satisfying to have</p> <ul style="list-style-type: none"> <li>the same qualitative and quantitative composition in terms of active principles/ substances</li> <li>the same pharmaceutical form</li> <li>of being bioequivalent</li> </ul> <p><i>(same composition and pharmaceutical form to be understood in a broad sense)</i></p>
Batch requirement	3 batches required	2 Batches for IR, 3 Batches for MR
BMR/ BPR	The exhibit, Intended BMR/ BPR required	BMR/ BPR Not required
DMF/ASMF	Open part of DMF is not required	The open part of ASMF is required
Process Validation	Not required	Required
Stability	6 months Accelerated, 6 months Long-term (new guideline)	6 months Accelerated, 6 months Long-term
Bioequivalence	The absence of a significant difference in the rate and extent, to which the active ingredient or the active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study.	Bioavailability of two medicinal products being similar to such degree, that their effects, with respect to both safety and efficacy is essentially the same. The medicinal products must contain the same active substance as defined above but may vary as regards the pharmaceutical form and strength.
Data protection	5 years	6 – 10 years From Nov.2005: 10 years + 1 year for an additional indication, submission of applications after the first 8 years

Bolar provision	Yes	No, from Nov. 2005: Yes
Authority	FDA (CDER, Office of generic drugs)	EMA and national authorities
Application	ANDA, CTD format, eCTD accepted	CTD, eCTD
Review time	12 -24 months	135 – 300 days depending on the procedure
Validity of the marketing authorization	Unlimited, annual reports to be provided including Pharmacovigilance data	To be renewed all 5 years including Pharmacovigilance data, annual reports products authorized by the centralized procedure, from Nov. 2005 still one renewal after 5 years, the unlimited validity
Registration Fees	Fees required for generic drugs as per GDUFA (Generic Drug User Fee Act)	Centralised Procedure: 1 strength and pharm. Form (basic): 116 000 €, per additional strength and form: 23200 €, each additional presentation per strength and form: 5 800 €, Annual fee: 75 600 € for all authorised presentations MRP, DCP, national applications: Depending on national regulations

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