

**ESTABLISHING REGULATORY PATHWAY FOR  
ESTABLISHMENT LICENSING SYSTEM:  
A PROGRESSIVE APPROACH**



**11-02-2020**

## **Acknowledgement**

I would like to thank DRAP for providing me an opportunity for this work in particular National Health Services Regulations and Coordination. My Special thanks to Honorable Minister Dr. Zafar Mirza to provide me his support and direction to work on this project.

## Table of Content

	<b>TITLE</b>	
<b>ESTABLISHING REGULATORY PATHWAY FOR ESTABLISHMENT LICENSING SYSTEM: A PROGRESSIVE APPROACH.</b>		
<b>1</b>	Acronyms	4
<b>2</b>	Executive Summary	5
<b>3</b>	Overview and Rationale for Change	6
<b>4</b>	Introduction	6
<b>5</b>	Objective	7
<b>6</b>	Scope	7
<b>7</b>	Progressive Licensing System	8
<b>8</b>	Inspection Policy	8
<b>8.1</b>	Inspection Process	8
<b>8.2</b>	Risk Observations	9
<b>8.3</b>	Rating of Inspection	9
<b>8.4</b>	Inspection Frequency	10
<b>8.5</b>	Duration of Inspection	10
<b>8.6</b>	Type of Inspection	10
<b>9</b>	Inspection of Foreign Establishment	10
<b>10</b>	Proposed Compliance and enforcement Directorate	11
<b>11</b>	Attachments Annex 1, 2, 3	12

## **1. Acronyms:**

**ELS:** ESTABLISHMENT LICENSING SYSTEM

**EEA – EFTA:** European Economic Area – European Free Trade Association

**ICH:** International Council for Harmonization

**PIC/S:** Pharmaceutical Inspection Cooperation/ Scheme

**SRAs:** Stringent Regulatory Authority

**WHO:** World Health Organization

**NC:** Non-Compliant

**C:** Compliant

**API:** Active Pharmaceutical Ingredients

**CoC:** Certificate of Compliance

**GMP:** Good Manufacturing Practices

**OTC:** Over The Counter Drugs

**N/R:** Not related

## **2. EXECUTIVE SUMMARY:**

This document presents the work conducted in light of international requirements and the non-compliance of a number of manufacturing facilities in Pakistan which are holding manufacturing licenses. This work consists of a series of documents provided to DRAP for the implementation of a revised licensing system. This work includes the following important aspects for consideration (Revision of Drug Licensing Rules 1976 chapter I & II) with the following changes:

- Definitions (Chapter I) to meet the current requirements of WHO GMP.
- Licensing system (Chapter II)
- User fees for different types of licenses (As approved by the Policy Board)
- Duration of license from five years to three years based on cGMP compliance

*Separate licenses will be issued for the followings:*

1. License to manufacture of finished products
2. License to manufacture API/drug substance [ICH Q7/WHO Guidelines]
3. License to perform independent manufacturing process activity
4. License to perform independent testing of drugs
5. License to perform independent packaging & labeling
6. License to distribute drugs
7. License to import drug products
8. License for compounding under cGMP

Considering the existing non-compliance status of many facilities a progressive licensing system has been introduced where licenses will be issued and the emphasis will be placed for more voluntary, progressive compliance and enforcement measures.

Progressive establishment licenses holder is required to meet all the elements of cGMP, maintain QMS in accordance with ICH guidelines and be responsible for gradual fulfilling all the conditions given at the time of inspection.

Inspection system and reporting format have been revised to meet and maintain appropriate compliance requirements in-line with international standards.

### **3. OVERVIEW AND RATIONALE FOR CHANGE:**

The existing licensing system is not in-line with the international standards and at the same time limited to manufacturing facilities both for Finished Products and APIs. While establishment licenses are issued to all pharmaceutical manufacturing, processing, testing, packaging, importing, and storages etc. There are specific sections within the good manufacturing practices guidelines which are directly related with all the activities (for details please see Annex 1 for GMP activities)

In existing licensing system there is no uniformity, consistency, transparency and accountability of regulatory requirements; at the same time the GMP inspections varies significantly. This issue has been highlighted significantly during the special inspection of **Earnest Young** organized by Government of Punjab. It is for that reason the pharmaceutical industry compliance with respect to GMP at this time is highly questionable.

It is considered that in order to achieve PIC/s membership a consistent uniform approach is needed for all activities with respect to control the life cycle of pharmaceutical products. Considering a significant variation in the GMP compliance of the manufacturing facilities, a progressive licensing system based on risk management is being introduced.

### **4. INTRODUCTION:**

During the past decade, there has been an increasing concern with the compliance of establishment facilities responsible for manufacturing, testing, packaging, importing, distributing and wholesaling of their products. This trend towards the frequent non-compliance needs to be properly addressed in compliance to full GMP requirements. In recent times, there are many issues including data integrity, compliance and enforcement globally.

The recent trend of out-sourcing many activities such as testing, packaging, importing, distribution and whole selling becomes very critical and requires appropriate licensing based on cGMP compliance.

Inspection process is used to assess the compliance of the premises, according to requirements of Drug Act 1976 and the Rules, meeting current WHO Good Manufacturing Process.

Inspectors are designated under section 17 of Drug Act 1976 and DRAP Act 2012.

The objectives of inspection are to:

- Minimize the health risk throughout the drug supply chain.
- Ensure that all activities of manufacturing process, packaging / labeling, testing, import and distribution and storage complies with cGMP requirements.
- Take compliance and enforcement actions when required.
- Maintain transparency, consistency and compliance of standards.

## **5. OBJECTIVES:**

The role of DRAP is to ensure that all establishments comply with the Risk Based current Good Manufacturing Practices requirements and maintain a balance between the potential health benefits and Risks posed by the therapeutic products. In order to comply the international standards and requirements it is essential that the licensing rule (1976 Chapter I&II) should be revised to include all activities which are part and parcel of safety, efficacy and quality of therapeutic goods. Based on these the objective of this document is to:

- Provide a revised and updated proposed licensing system for DRAP based on the progressive licensing system.
- Improve the inspection system in-line with international standards so that to achieve the PIC/S membership within a reasonable time period.

## **6. SCOPE:**

The scope of establishing system will be applicable to the premises where therapeutic goods are manufactured, processed, packaged / labeled, tested, imported, distributed and stored (**Table 1**).

**Table 1: Licensable activities by type of establishment**

<b>Establishments</b>	<b>Manufact urer/ Processor</b>	<b>Packager/ / Labeller</b>	<b>Importer</b>	<b>Distribut or</b>	<b>Compo under</b>	<b>Tester</b>
Domestic – Finished Dosage Forms						
Domestic – Active Pharmaceutical Ingredients					N/A <sup>2</sup>	
Foreign <sup>1</sup>			N/A <sup>2</sup>	N/A <sup>2</sup>	N/A <sup>2</sup>	

<sup>1</sup> Foreign establishment will not be issued establishment license however their license will be included in the domestic license holder.

<sup>2</sup> These facilities / activities will not receive the establishment license.

DRAP is committed to ensure that therapeutic products are safe for the consumer and patients by managing the health-related risk and benefit of therapeutic products by:

- Minimizing health risk
- Maximizing safety and Quality
- Providing clear and accurate information

Before therapeutic goods can be sold, they must meet the standards of safety and quality where they are produced either domestically or by foreign manufacturer. It is also important that the raw materials should be properly controlled in a complex global supply chain as Pakistan relies on the supply of these materials from other countries.

It is important that uniform application of cGMP requirements must be applied both domestically and by foreign establishments. cGMP as outlined in Drug Act must be applied in order to issue the establishment license.

## **7. PROGRESSIVE LICENSING SYSTEM:**

Progressive Licensing System is developed as a strategy for the modernization of the framework for the regulation of the therapeutic goods. The Drug Rules (Chapter II) for existing licensing are required to be updated in light of the proposed progressive licensing system. The intent is that the Pakistan Regulatory requirements should be in line with the international standards. Emphasis will be placed on internal and external training to ensure that the expectations are clear and fulfilled. The proposed progressive licensing system will issue licenses to establishments supported by new prohibitions and conditions. This will create an introduction of more flexible compliance and enforcement measure and at the same time increase in maximum fines and penalties.

An establishment license would be required for the following activities;

- Manufacturing of Finished products
- Manufacturing of APIs / Drug Substance
- Processing
- Packaging
- Testing
- Importing
- Distributing
- Compounding

Any other processes that have direct impact on the safety and Quality of products for example, Sterilization Processes.

In the new progressive licensing system new licenses will be issued based on the elements as specified in the table-1 as annexure-I for the period of three years. All these licenses are based on cGMP and QMS. If an establishment does not comply with the requirement of cGMP and QMS they will be given an opportunity to bring their establishment into compliance standards. This opportunity will be given only two times and if the violation still exists, their licenses will be suspended/cancelled.

Progressive establishment licenses holder is required to meet all the elements of cGMP and maintain QMS in accordance with ICH guidelines and responsible for fulfilling all the conditions required by the regulations.

## **8. INSPECTION POLICY:**

The inspection policy is risk based where frequency and duration is based on the inherent risk pose by the nature of activities performed and the compliance history of the establishment. If compliance is identified or mitigation strategy is needed more frequent inspections will be performed as a general rule fully compliance facility will be inspected every two to three years.

Foreign facilities must also comply with the GMP requirements before they are listed in the drug establishment license in order to sell the product in Pakistan. Inspection results from the following international regulatory authority along with proper evidence will be acceptable however if there is a compliance issue of a specific facility it will be right of DRAP to inspect the facility before inclusion into the license;

- WHO pre-qualified facility
- ICH regions / SRAs countries
- Member of PIC/S
- DRAP will also perform onsite inspection if required.

### ***8.1 Inspection Process:***

The inspection activity will be planned in advance by the inspection division. A proper notification will be issued to establishment with respect to their inspection schedule. The inspection division may also request the establishment to provide certain information in advance (e.g., site master file or outline of the facility). Advance notice may not be given if there is an immediate risk to health and safety and immediate investigation is needed.

Once the date of inspection has been set, the establishment is informed about the inspection date and time. For any changes in the inspection date with proper justification from the establishment, this will only be accepted at the discretion of DRAP.

The detail of an inspection procedure is outlined in the Standard Operating Procedure (SOP No. ID/SOP/IP001). During an inspection, DRAP inspectors will observe and discuss the various elements of cGMP and will review records, documents and procedures. The inspection will be in detail, rigorous and follow the cGMP including QMS. Following elements will be included in inspection:

- Pharmaceutical Quality system
- Facility Design
- Integrity of Data and Record keeping
- Qualification and Validation Processes
- Equipment Qualification and maintenance
- Staff training
- SOPs
- Supplier Qualification
- Raw material Control
- Storage facilities
- Processing Operations
- Environmental and Contamination Control
- Sanitary conditions
- Product Testing and Stability
- Packaging
- Distribution

## ***8.2 Risk Observation:***

Inspector will make observations where establishment is not meeting regulatory requirements. Based on the level of risk they will be classified as:

Critical observation: Describe a situation that is likely to result in a product failure or serious health risk and also involve in fraud and falsification.

Major Observation: Describe a situation that may result in the non uniformity of activity that may have an impact on the quality/safety of therapeutic product.

Other Observation: Describe a situation that is neither critical nor major but is a departure from GMP guidelines.

### ***8.3 Rating of Inspection:***

The establishment is rated based on the risk level of observation at the time of **inspection**. They are as follows:

**Compliant (C):** If the establishment meets all the requirements it will be considered as compliant.

**Not- Rated (NR):** if the establishment not meeting the requirements but committing for correction within the agreed time.

**Non-Compliant (NC):** If the establishment is not meeting the requirements it will be considered as non-compliant.

Under the progressive licensing system, establishment will be given opportunity to bring their establishment so that they meet the GMP requirements along with the QMS. It is the objective of the system to assign Non-Rated status to those establishments which are under improvement through proper time line of CAPAs issued to them.

A voluntary compliance system will be introduced for establishment, that receives an NR rating. It is expected that establishment will provide a plan which will be approved by the DRAP to bring the establishment to a compliant rating. these establishments will be inspected again after the completion date of approved CAPA.

In case establishment was unable to bring their establishment fully compliant DRAP may consider enforcement action. This will include the suspension of establishment licensing

**period.** Proper policies and directive will be developed for the compliance and enforcement plan.

End of Inspection: Inspector / Inspection Team will discuss the observation with the management during the exit meeting. The final report will be forwarded to the manufacturer within thirty days. The report will include all the observations discussed during the exit interview.

Inspection Report: The lead inspector after having discussion with other member of the team will develop a report of inspection. This report will be submitted to the Director of inspection division.

Inspection Committee: An inspection committee consisting of lead inspectors and expert (as required) will review all reports of lead inspectors and will finalize all the observation after thorough discussion in order to create uniformity in the inspection system. In final letter will be developed and will be forwarded to the company outlining all the observations identified in the inspection. The establishment will be given thirty days to develop CAPA for each observation including its effectiveness in time line. This response will again be reviewed by the lead inspector and team before it is accepted. In case if an advice is required, a committee may meet again to review the report. For any additional information about QRM and CAPA, please refer to ICH Q9 and Q10.

DRAP will post on its website an inspection report excluding its proprietary information.

#### ***8.4 Inspection Frequency:***

DRAP will inspect establishment against cGMP standard along with QMS to verify that Quality and Safety standard are met by the establishment before drugs are sold to public. The frequency of inspection will be based on the licensed activities and level of risk but also at the same time the consideration of resources and priorities. More frequent inspection may occur when risk has been identified based on:

- Current status of compliance and compliance history
- Size/activity of the establishment
- Type and risk of activities
- Supply chain importance

## **8.5 Duration of Inspection:**

An average time required for inspection is usually five days but is based on the:

- Size of the establishment
- Type of the establishment
- Risk of the activities
- Compliance history

In general, a typical inspection may require more than five days, which includes both pre, & post inspection meetings.

## **8.6 Type of Inspection:**

Following are the types of inspection:

Initial Inspection: This is the first inspection conducted at an establishment before issuing the license.

Regular Inspection: An inspection that is conducted against all applicable requirements of cGMP along with QMS and focus on the risk and the systems of controls in place at the establishment.

Re-inspection: This is a follow up inspection carried out in response to the assignment of a Non-Rated (NR) / non-compliant (NC) inspection rating.

Re-Assessment: This is a follow-up inspection carried out in response to the assignment of an overall compliant (C) inspection rating on the previous inspection where number and type of observation require corrective action in a timely manner.

## **9. INSPECTION OF FOREIGN ESTABLISHMENT:**

Foreign establishment must comply with the cGMP requirements so that the establishment is listed along with the domestic establishment license. Foreign inspection will also be conducted based on the risk, country and its regulatory authority status. This approach considers other things like:

- Type of cGMP evidence for the foreign side

- cGMP compliance history
- The date that new cGMP evidence is required

There is also requirement of a Quality Agreement between importer and exporter. Foreign Inspection will be exempted for SRAs Countries, PIC/S member countries, WHO Pre-qualified facilities and or well-established forum such as EEA - EFTA. It should be noted that the option of having foreign inspection will be reserved with DRAP to inspect the facility before inclusion into the license if there is a compliance issue of a specific facility.

## Annex 1

GMP Regulations by Activity for Issuance of License							
Section	M-FDP	MDS	TL	PL	D	I	C
Pharmaceutical quality system	✓	✓	✓	✓	✓	✓	✓
Good manufacturing practices for pharmaceutical products	✓	✓					
Sanitation and hygiene	✓	✓	✓	✓			✓
Qualification and validation	✓	✓	✓	✓	✓		
Complaints	✓	✓	✓	✓	✓	✓	✓
Product Recall	✓	✓	✓	✓	✓	✓	✓
Contract production, analysis and other activities	✓	✓	✓	✓		✓	
Self-inspection, quality audits and suppliers' audits and approval	✓	✓	✓	✓	✓	✓	✓
Personnel	✓	✓	✓	✓	✓	✓	✓
Training	✓	✓	✓	✓	✓	✓	✓
Personal hygiene	✓	✓	✓	✓	✓		✓
Premises	✓	✓	✓	✓	✓	✓	✓
Equipment	✓	✓	✓	✓			✓
Materials	✓	✓	✓	✓	✓		✓
Documentation & record	✓	✓	✓	✓	✓	✓	✓
Good practices in production	✓	✓					✓
Good practices in quality control	✓	✓	✓	✓	✓		

\*M-FDP : Manufacturing of Finished Drug Product

\*MDS : Manufacturing of Drug Substance

\*TL : Testing Laboratories

\*PL : Packaging and Labelling

\*D : Distributor

\*I : Importer

\*C : Compounder