PIC/S: TRAINING THE REGULATORS TO REGULATE cGMP COMPLIANCE

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REVIEW ARTICLE

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ABSTRACT

PIC/S is an international Organization for implementing cGMP standards in its member countries. The basic objective of PIC/S is to improve and standardize cGMP compliance in member countries. Their aim is to enhance GMP intelligence via sharing of GMP inspection reports. Further it wants to reduce duplication of inspections to save the cost and time.

Their regulations are directed to promote harmony in GMP standards and to train national regulatory authorities for cGMP vigilance. They requires that every nation shall empower the legislation to inspect the facilities as per definite program, to issue notices for noncompliance, to impart regular training to all concerned employees.

Keywords: cGMP, GMP, PIC/S, OOS, Compliance, Inspection.

INTRODUCTION

All nations in the world are not alike in their skills and mode for cGMP compliance. A need for international body was felt to harmonize the implementation and audit of cGMP standards. PIC/s is the international training forum run jointly by Regulatory Authorities in Europe to harmonize cGMP standards. It promotes the uniform interpretation/implementation of GMP and Quality Systems as applicable to Pharmaceutical and API manufacturing. PIC/S has issued extensive guidelines on GMP Inspection/vigilance to health authorities in European countries.

PIC/S GUIDELINES

PIC/S guidelines are based on twenty major attributes of GMP administration and compliance. (1-2) unlike other guidelines PIC/S guidelines are not directed towards the industry and Pharmaceutical professionals. However, these are designed for health authorities to improve and maintain cGMP Compliance. (3-5)

Power of Legislations

Every nation shall empower "cGMP legislation" to ensure compliance without any conflict of interest. The legislations must clearly explain the scope of "current GMP Requirements". The legislation shall power the inspectors as per below (6):

- Each inspector shall have proper identity, authority and jurisdiction with respect to enter at any reasonable time in any place (including private dwelling) where drugs/medicinal products are manufactured, imported, exported, packaged, released, stored or tested.
- He shall have power to withdraw samples for submission to designated laboratory.
- He shall have authority to make copies of documents and photographs of drug/medicinal product premises and equipment as required.
- He shall have power to examine any receptacle or package that contains articles subject to legislation.
- He has authority to seize or detains a drug/medicinal product or related article believed to be in violation.
- He shall have authority to enter in a Further each manufacturer that manufacture (total or partial), package/label, import, export (including export only), distribute and test drugs shall have obligation to cooperate and not to obstruct an inspector.
- He must have entitlement to report serious adverse drug/medicinal product reactions and manufacturer to report any product

defect to notify a competent regulatory authority.
- He can order recall and hold manufacturing authorizations.
- He shall have power to notify the regulatory authority of significant changes or of conditions which can affect the quality, safety or efficacy of a drug/medicinal product.
- He shall hold authority to record the manufacturing activities.
- He can order to stop sale and processing of drugs/medicinal products under unsanitary conditions leading to adulteration.
- He can advise prosecution and / or penalties upon conviction.
- He can examine any product design for local distribution or for exports.
- He has authority to check conflict of interest for cGMP compliance by management.

Directives and Policies

Each nation must have well structured body and SOPs to implement cGMP. The SOPs shall include the followings:

1. Procedure for designating inspectors
2. Procedures for enforcement of cGMP
3. Code of conduct/ Code of ethics for regulatory inspections
4. Procedures for Training the Inspectors
5. Policies for Alert/crisis management

GMP standards

Each nation must have adequate GMP standards with special attention on "Process validation" in detail. The Scope of GMP for different categories of the products shall be distinctly provided.

The Qualifications and Training of Inspectors

Each nation shall decide on minimum qualifications, duties and training requirements for GMP inspection staff. The regulations shall define the necessary Training programme and mechanism to evaluate the effectiveness of trainings executed. There shall be a mechanism to assure effectiveness of training programme.

Inspection Procedures

Each country shall have well defined Inspection strategy. It must establish plans that describe the duties and responsibilities of the inspecting staff, objectives for inspection, and resources applied to fulfill the audits. Typically, each nation shall have SOPs for:

- Pre-inspection preparation
- Format and content of inspection
- Inspection procedures
- Post-inspection activities
- Storage of inspection reports

Inspection Performance Standards

Each country must have performance standards for GMP Inspections. The same shall include the followings:

- Suitability of operating staff , machines and raw materials for manufacturing drug products.
- Integrity and completeness of SOP and records.
- Integrity of all machines, analytical methods, manufacturing procedures through validation studies.
- Integrity of manufacturing areas with respect to sanitation, hygiene, design, temperature, humidity, air changes and access control.
- Integrity of critical systems such as Water Systems and AHY systems.
- Data integrity aspects
- Integrity of critical procedures such as OOS, Deviation Control, Change Control, Recall Procedures.
- Integrity and storage system for data generated during production, storage, quality control of the drug products.

Enforcement Powers, Procedures and Policies

The regulatory authority in each country shall have adequate powers for the following administrative actions:

- To issue notifications against violations of cGMP.
- To respond to the appeals raised by the affected parties.

- To penalize the defaulters.
- To refuse the review for deficient applications.
- To suspend/cancel the licenses of habitual defaulters.

Guidelines for evaluating alert and crisis management systems for Inspectors

Each regulatory authority must train her inspectorate to evaluate and manage crisis in drug manufacturing and distribution. The inspectorates must have sufficient knowledge and experience to issue alerts and to prompt recall of the faulty products.

cGMP assessing capability

Each authority shall have experienced staff and facilities to assess the quality of the drug products and validating the analytical procedures.

Surveillance Programme evaluations

Each authority shall have trained staff for sampling of the drug products for verification of the quality and recall monitoring. In addition there shall be a system to register and investigate consumer complaints**.** The adverse reaction/drug defects reporting system/ procedures shall be also part of surveillance program.

Guidelines for evaluating Quality Management System

Each country shall have pre-inspection program to evaluate the GMP compliance history, critical activities and type(s) of dosage forms manufactured at the site.

Guidelines for conducting Pre-Inspections

Each regulatory authority shall draw detailed scope for pre-inspection activities.

The inspection plan shall be based on the company's GMP compliance history, critical activities and type(s) of dosage forms manufactured.

Format and content of Inspection Reports

Each country shall ensure that:

- The precise format for inspection and detailing inspection reports is available.
- The observations are factual and are based on proper interpretation of applicable legislation.
- The observations are classified/ categorized according to risk.
- The overall compliance rating is determined based on the inspection findings.
- The inspection reports are prepared and submitted to the higher authorities.

Inspection Methodology

Each health authority shall ensure that there is well defined SOP for conducting inspections.

The SOP must details the requirements for conducting inspections.

The inspections must include assessment of critical stages and parameters of manufacturing processes and Validation.

The inspections must design the inspection plan based on the compliance history and type of the products manufactured at the site.

Post-Inspection activities

There shall be a procedure for reviewing post-inspection report and issuing compliance notification appropriately

Storage of Inspection Data

Each health authority shall have policy/procedure for the storage of inspection data in a secure and controlled manner.

Performance Standards

Each health authority shall establish Inspection performance standards.

Enforcement Powers and Procedures

Each health authority shall maintain a list of valid and suspended authorizations. Further, there shall be written procedures for issuing notice for violations of cGMP Norms/ Recall of defective products/ Suspension of manufacturing authorization (or equivalent) and related GMP certificate / Seizure of fraudulent/falsified products/ Prosecution of defaulters.

Enforcement powers shall also include appeal procedures.

Each health authority shall have system to issue alerts/warnings as required. There shall be well established alert performance standards. The regulator shall have open access to contract laboratories capable of conducting necessary analyses. There shall be a mechanism to qualify such laboratories to recognized standards.

Guidelines for assessing analytical capability

Each health authority must verify the analytical capability of drug manufacturers. It may establish a system for approval of QC/QA staff.

Further there shall be a system to verify integrity of laboratory records, analytical methods and instruments. The procedures such as OOS, Change Control, Validation, Calibration and Data integrity shall be available as per ICH standards

Vigilance & Verifications

The health authorities must verify that:

- The surveillance programme covers API as well as dosage forms.
- Technical and regulatory performance for all the products is reviewed annually and records of review are maintained.
- A consumer complaint system/procedure and records are maintained.
- High risk issues are investigated immediately.
- The inspectors have adequate access to the market complaints.
- All reported products defects are documented and investigated.
- The investigators are aware of recognized international standard.
- The investigators are aware of Key performance indicators (KPI) for the overall GMP compliance.
- The investigators are capable of reviewing practical aspects of quality systems and documentation control system, quality audit plans and data integrity.

CONCLUSION

PIC/S is performing the most vital task of training the regulators. It has truly defined the essential procedures which the regulatory authorities shall follow to ensure cGMP compliance by the industry. PIC/S require that regulators must have adequate knowledge, system, training, powers, procedures and involvement to effectively ensure compliance.

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CONFLICT OF INTEREST

Author declares that there are no conflict of interest.

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