Collation, Compilation and Comparison of GLP Compliance Requirements to Support Regulatory Approvals for Select Category of Pharmaceutical Products in Selected Countries

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ABSTRACT
The present study activity to shed light on to the role of the GLP inspections which is helps to overcoming non-compliance activity. The objective of the present study is to identify the GLP inspection and understanding the underlying concepts for GLP compliance for licenses pertaining to Pre-Clinical study. The study compared and contrasted the GLP requirements and their inspection procedure of the regulatory authorities in India, EU & Singapore.

Keywords: GLP, Inspection, Compliance, Pre-clinical study.

INTRODUCTION
Good Laboratory Practice (GLP) is defined in the OECD Principles as “… a quality system concerned with the organizational process and the conditions under which non-clinical health and environmental safety studies are planned, performed, monitored, recorded, archived and reported”. The aim is to ensure the quality, reliability and integrity of studies allowing the reporting of verifiable conclusions and the traceability of data. It must be noted that GLP is not directly concerned with the scientific design of a study and, it is also important to differentiate between the formal regulatory terms “Good Laboratory Practice” as opposed to the general application of “good practices” in scientific investigations. [1] Good Laboratory Practice studies that support or are intended to support application for research or marketing permits for the following products:

- food and color additives
- human and animal drugs
- medical devices for human use
- biological products

**Good Laboratory Practice stresses the importance of the following main points**
- Resources : Organisation, Personnel, Facilities, Equipment
- Rules : Protocols, Standard Operating Protocols (SOPs), Study Director as pivotal point of study control
- Characterisation : Test items, test systems
- Documentation : Raw data, Final report, Archives
- Quality Assurance : Independent from study conduct.[1]

**Example:** Non-compliance GLP USFDA issue a warning letter to GLP laboratory for non-compliance.

**Reason:**
- Quality Assurance Unit failed to be entirely separate from and independent of the personnel engaged in the conduct of that study.
- Quality Assurance Unit failed to assure that the final study report accurately described the methods and Standard Operating Procedures, and that the reported results accurately reflect the raw data.
- Testing facility failed to establish standard operating procedures for data handling, storage, and retrieval. [2]

**Materials or Data source**
The current study search is done using different resources like Pharmaceutical Review articles, Public domains, Journals and Regulatory Authority websites,
- Guidelines and/or regulation documents from the Regulatory Authorities
- ICH & WHO Guidance documents

RESULTS AND DISCUSSION

**Inspection Observation:**
- No deviation: Approval / grant of license-Study Continue.
- Deviation: Rejection-CAPA-satisfied- Approval / grant of license-Study Continue.

**EMA GLP Inspections:**
- Pre-inspection - to determination of the laboratory’s compliance with the GLPs test facilities to conduct a pre-clinical study as per the requirements.
- Routine/general inspection - To determination of a laboratory's compliance with the GLPs, it includes
- examination of an ongoing study as well as a completed study
- A Special inspection - any of a series of inspections conducted for various compelling reasons

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➢ (questionable data in a final report, tips from informers, etc.)

➢ A follow-up inspection - an inspection made sometime after a GLP inspection which revealed objectionable practices and conditions. The purpose of the follow-up inspection is to assure that proper corrective actions have been taken.

**Inspection Observation:**

➢ Critical (CR): Conditions, practices or processes that adversely affect the rights, safety or wellbeing of the subjects and/or the quality and integrity of data. Critical observations are considered totally unacceptable. - study stop - suspension of the GLP laboratory.

➢ Major (MA): Conditions, practices or processes that might adversely affect the rights, safety or wellbeing of the subjects and/or the quality and integrity of data. Major observations are serious deficiencies and are direct violations of principles. Data may be rejected and/or legal action required. - study stop but submit the CAPA - study continue.

➢ Minor (MI): Conditions, practices or processes that would not be expected to adversely affect the rights, safety or wellbeing of the subjects and/or the quality and integrity of data. Observations classified as minor, indicate the need for improvement of conditions, practices and processes - study continue but submit the CAPA.

**Deviations**

Critical deficiency

A critical deficiency is one which seriously threatens the credibility of the Singapore GLP Compliance Programmed. It includes gross lack of technical competence, persistent violation of Procedures and Conditions, regulations, gross lack of commitment of the organization to quality or compliance with OECD GLP Principles and existence of serious doubt on the integrity and impartiality of the organization. A management system breakdown, as indicated by a series of significant deficiencies which seriously threaten the quality of all activities under the system, warrants a critical deficiency.

Minor - for a departure from the Principles which is not considered as a major deficiency. This may be a recommendation or a reminder for follow up review at the next inspection.

Significant deficiency

<table>
<thead>
<tr>
<th>SL.NO</th>
<th>Regulatory authority</th>
<th>Type of inspections</th>
<th>Inspection schedule</th>
<th>Observation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CDSCO &amp; SLA</td>
<td>Inspection before approval</td>
<td>Application for GLP license</td>
<td>No deviation Deviation</td>
</tr>
<tr>
<td>2</td>
<td>CDSCO &amp; SLA</td>
<td>Inspection for rejected application</td>
<td>Re-application after rejection</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>CDSCO &amp; SLA</td>
<td>Renewal inspection</td>
<td>Expiry of the license</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>CDSCO &amp; SLA</td>
<td>Inspection for specific reason</td>
<td>Specific reason</td>
<td></td>
</tr>
</tbody>
</table>

**Table 2: Factsheet GLP - EU**

PRODUCT CATEGORY: Chemicals, Biological drugs & Medical device

COUNTRY OF FILING: EU

REGULATING AGENCY: EMA

REGULATING MINISTRY: Science Medicines Health

INSPECTION BY: Committee for Medicinal Products for Human use (CHMP)

<table>
<thead>
<tr>
<th>SL.NO</th>
<th>Regulatory authority</th>
<th>Inspection Categories</th>
<th>Type of inspections</th>
<th>Inspection schedule</th>
<th>Observation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>EMA</td>
<td>Test facilities inspection/study audit</td>
<td>Pre- inspection</td>
<td>Before the approval to conduct the study</td>
<td>Critical (CR) Major (MA) Minor (MI)</td>
</tr>
<tr>
<td>2</td>
<td>EMA</td>
<td>Routine/general inspection</td>
<td></td>
<td>Any time</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>EMA</td>
<td>Special inspection</td>
<td>Specific Cause/Reason</td>
<td>Submit the CAPA to EMS</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>EMA</td>
<td>Follow up inspection</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
A significant deficiency has serious adverse effect on the validity of an activity, its results or the competence of the organization or a violation of SAC Procedures & Conditions for registration. The existence of a serious doubt on the technical validity of an activity or its raw data, reported studies, as indicated by a series of related minor deficiencies is a significant deficiency. Furthermore,
persistence of a minor deficiency for an extended period of time and without any plausible explanation may be a violation of SAC Procedures & Conditions for registration, warrants is a significant deficiency

Minor deficiency
A minor deficiency has no serious adverse effect on the validity of the activity, its results or the competence of the organization.

SUMMARY AND CONCLUSION
1. Understand the GLP regulatory compliance requirements in drug development process and marketing various Pharmaceutical Products.
2. Collation of compliance requirements for GLP inspection (pre-clinical study) in drug development.
3. Identify the inspection process which includes inspection types, inspection purpose, time of inspection, outcome of the inspection that occur in the pre-clinical site throughout the life cycle of a product from research & development to commercialization.
4. European Medicines Agency follows the OECD guidelines for the GLP requirements but GLP inspection have framed their own regulation and guidelines for identify the compliance and non-compliance activity in the EU.
5. CDSCO – India follows the Schedule L-I guidelines for GLP requirements and inspection are carried out by CDSCO/SLA for maintains of the compliance activity in the India and also take certificate from NGCMA to conduct a study.
6. Singapore Accreditation council (SAC) – Singapore follows the OECD guidelines for the GLP requirements but GLP inspection have framed their own regulation and guidelines for identify the compliance and non-compliance activity in the Singapore.

REFERENCE

Table 3: Factsheet GLP - Singapore[9]

<table>
<thead>
<tr>
<th>SL. NO</th>
<th>Regulatory authority</th>
<th>Type of inspections</th>
<th>Inspection schedule</th>
<th>Observation-Outcome</th>
</tr>
</thead>
</table>
| 1      | SAC                  | Preliminary inspection | Application for GLP certification | Review the documents
All satisfied – approval for initial inspection (site inspection)
Not satisfied- retune to the applicant. |
| 2      | SAC                  | Initial inspection  | After the clearance from preliminary inspection | No deviation- GLP certificate granted.
Deviation - submit the CAPA to SAC-no deviation - GLP certificate granted |
| 3      | SAC                  | (Surveillance inspection) Routine study audit | First anniversary of the initial on-site inspection | No deviation - GLP certificate confirmed.
Deviation – submit the CAPA to SAC-no deviation - GLP certificate confirmed. |
| 4      | SAC                  | (Surveillance inspection) Full inspection | Second anniversary of the initial on-site inspection and every two years | No deviation- GLP certificate confirmed. |
| 5      | SAC                  | Special inspection  | Specific Cause/Reason | No deviation- GLP certificate confirmed. |
| 6      | SAC                  | Follow up inspection/Verification inspection | After submit the CAPA to authority | Deviation (Critical or Significant) - suspension – new application- after one form the date of subsection. |
Figure 3: Inspections to grant a GLP certificate-Singapore

4. Health MOF. the Drugs and Cosmetics Act and Rules. 2005;1940. Available from:
Figure 4: Inspections to confirm a GLP certificate (studies continue)-Singapore.


10. Registration GLP. Compliance Programme
Table 4: Compilation of Good Laboratory Practice Compliance (Pre-Clinical study)

<table>
<thead>
<tr>
<th>Country</th>
<th>India</th>
<th>European Union (EU)</th>
<th>Singapore</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regulatory Agency</td>
<td>Central Drug Standard Control Organization (CDSCO) / SLA</td>
<td>European Medicines Agency (EMA)</td>
<td>Singapore Accreditation council (SAC)</td>
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<tr>
<td>Regulations</td>
<td>Schedule L-I</td>
<td>DIRECTIVE 2004/10/EC and OECD GLP guidelines</td>
<td>OECD GLP guidelines</td>
</tr>
<tr>
<td>Dosage Forms covered</td>
<td>Chemicals &amp; Biological Drugs</td>
<td>Chemicals &amp; Biological Drugs</td>
<td>Chemicals &amp; Biological Drugs</td>
</tr>
<tr>
<td>Classification Of Inspection</td>
<td>Inspection before approval inspection</td>
<td>Pre- inspection</td>
<td>Preliminary inspection</td>
</tr>
<tr>
<td></td>
<td>Inspection for rejected application</td>
<td>Routine/general inspection</td>
<td>Initial inspection</td>
</tr>
<tr>
<td></td>
<td>Renovation inspection</td>
<td>Special Inspection</td>
<td>Routine study audit</td>
</tr>
<tr>
<td></td>
<td>Inspection for specific reason</td>
<td>Follow up inspection</td>
<td>Special inspection</td>
</tr>
<tr>
<td>Inspection Frequency</td>
<td>Once in a year</td>
<td>Every 12 to 30 months once</td>
<td>Once in a year</td>
</tr>
<tr>
<td>Inspection Done By</td>
<td>CDSCO &amp; SLA</td>
<td>Committee for Medicinal Products for Human use (CHMP)</td>
<td>SAC</td>
</tr>
<tr>
<td>Classification of Observations</td>
<td>Critical</td>
<td>Major</td>
<td>Critical</td>
</tr>
<tr>
<td></td>
<td>Major</td>
<td>Minor/Others</td>
<td>Significant</td>
</tr>
<tr>
<td>Consequences</td>
<td>Query letter / Clarification letter</td>
<td></td>
<td>Minor</td>
</tr>
<tr>
<td>Inspection Fee</td>
<td>Rs. 6000</td>
<td></td>
<td>$ 1000 per person/per day.</td>
</tr>
<tr>
<td>Inspection Report type</td>
<td>Inspection report</td>
<td>Inspection report</td>
<td>Inspection report</td>
</tr>
</tbody>
</table>

11. GLP01 - Procedures and Conditions for.
2014;(November):1–18. Available from: