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Review Article

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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Table 1: Factsheet GLP - India[3], [4], [5] List of types of Inspections GLP-INDIA

PRODUCT CATEGORY : Chemicals & Biological drugs
COUNTRY OF FILING : India
REGULATING AGENCY : CDSCO / SLA
REGULATING MINISTRY : Ministry of Health and Family Welfare
INSPECTION BY: CDSCO & SLA

SL.NO	Regulatory authority	Type of inspections	Inspection schedule	Observation
1	CDSCO & SLA	Inspection before approval	Application for GLP license	No deviation Deviation
2.	CDSCO & SLA	Inspection for rejected application	Re-application after rejection	
3.	CDSCO & SLA	Renewal inspection	Expiry of the license	
4.	CDSCO & SLA	Inspection for specific reason	Specific reason	

- (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 2: Factsheet GLP - EU[6], [7], [8] List of types of Inspections 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)

SL.NO	Regulatory authority	Inspection Categories	Type of inspections	Inspection schedule	Observation
1.	EMA	Test facilities inspection/study audit	Pre- inspection	Before the approval to conduct the study	Critical (CR) Major (MA) Minor (MI)
2.	EMA		Routine/general inspection	Any time	
3.	EMA		Special inspection	Specific Cause/Reason	
4.	EMA		Follow up inspection	Submit the CAPA to EMS	

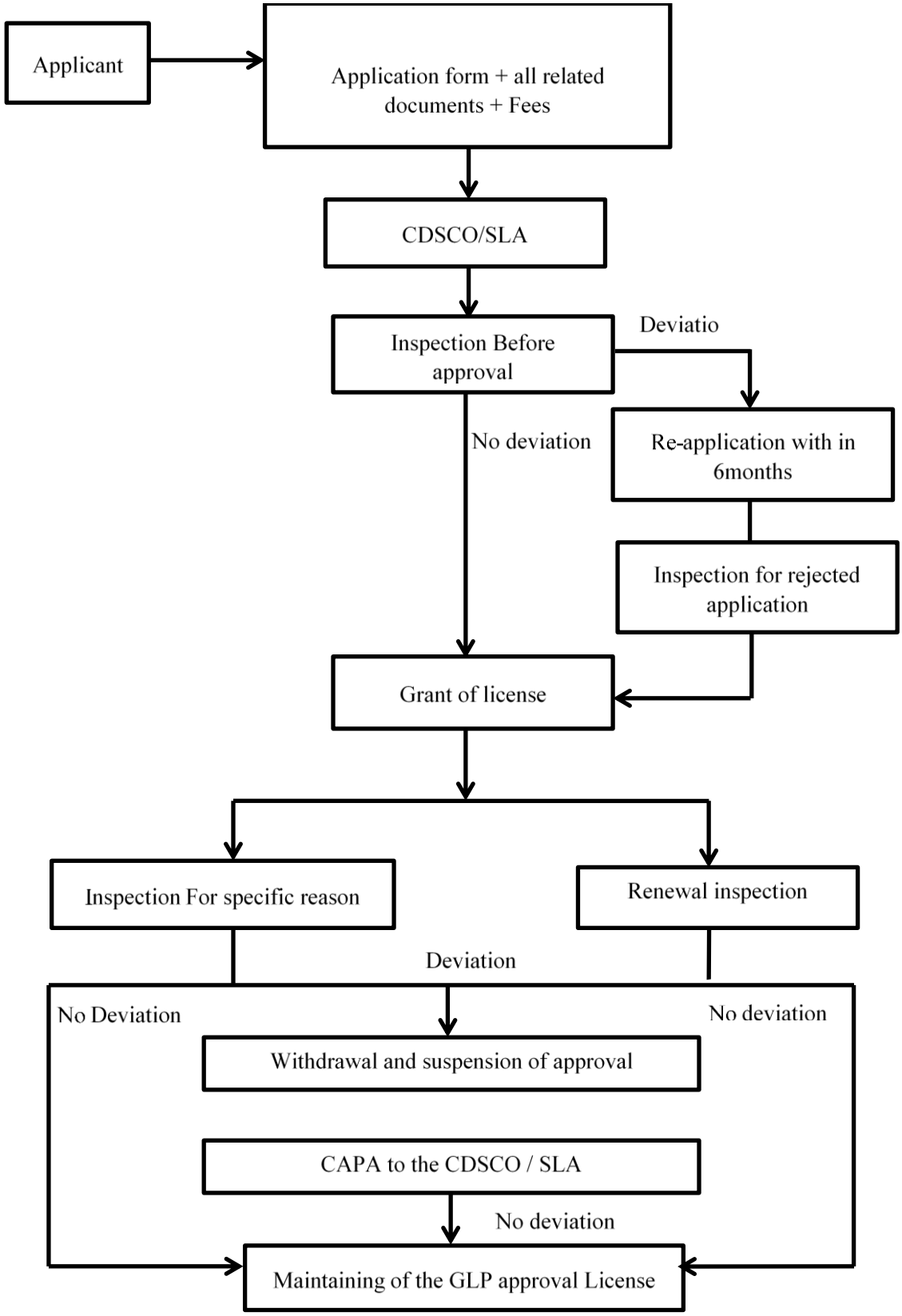

Fig 1: Inspection for obtaining GLP License-India

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,

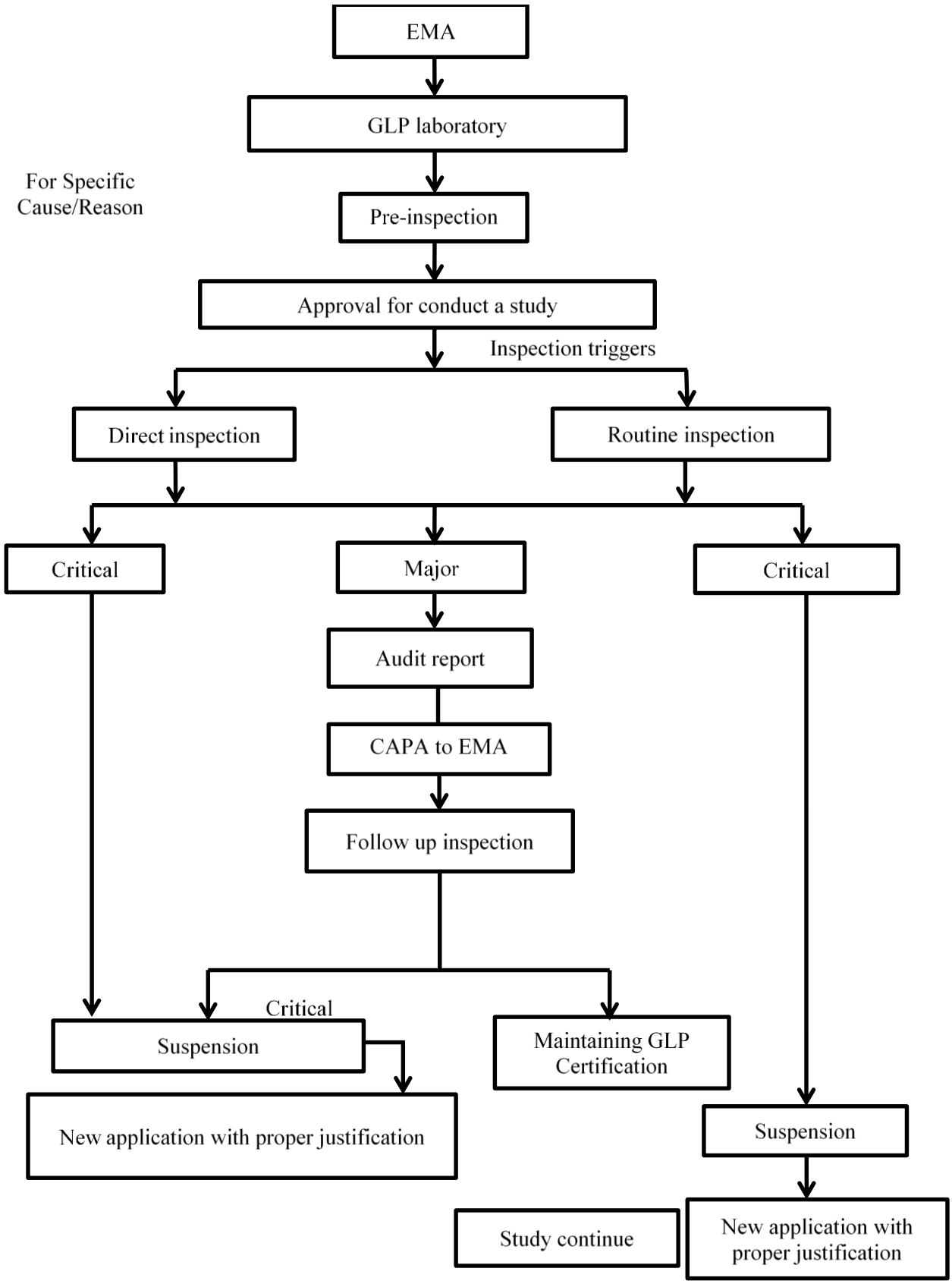

Figure 2: GLP inspection EU

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

Table 3: Factsheet GLP - Singapore[9]

List of types of Inspections GLP-Singapore
PRODUCT –CATEGORY : Chemicals & Biological drugs
COUNTRY OF FILING : Singapore
REGULATING AGENCY : Singapore Accreditation Council (SAC)
REGULATING MINISTRY : Ministry Of Trade And Industry (MTI)
INSPECTION BY : SAC

SL. NO	Regulatory authority	Type of inspections	Inspection schedule	Observation-Outcome
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	
4.	SAC	(Surveillance inspection) Full inspection	Second anniversary of the initial on-site inspection and every two years	No deviation - GLP certificate confirmed. Deviation – submit the CAPA to SAC-no deviation - GLP certificate confirmed.
5.	SAC	Special inspection	Specific Cause/Reason	
6.	SAC	Follow up inspection/Verification inspection	After submit the CAPA to authority	No deviation- GLP certificate confirmed. Deviation (Critical or Significant) - suspension –new application- after one form the date of subsection.

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
4. site throughout the life cycle of a product from research & development to commercialization.

- 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.
- 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.
- 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.

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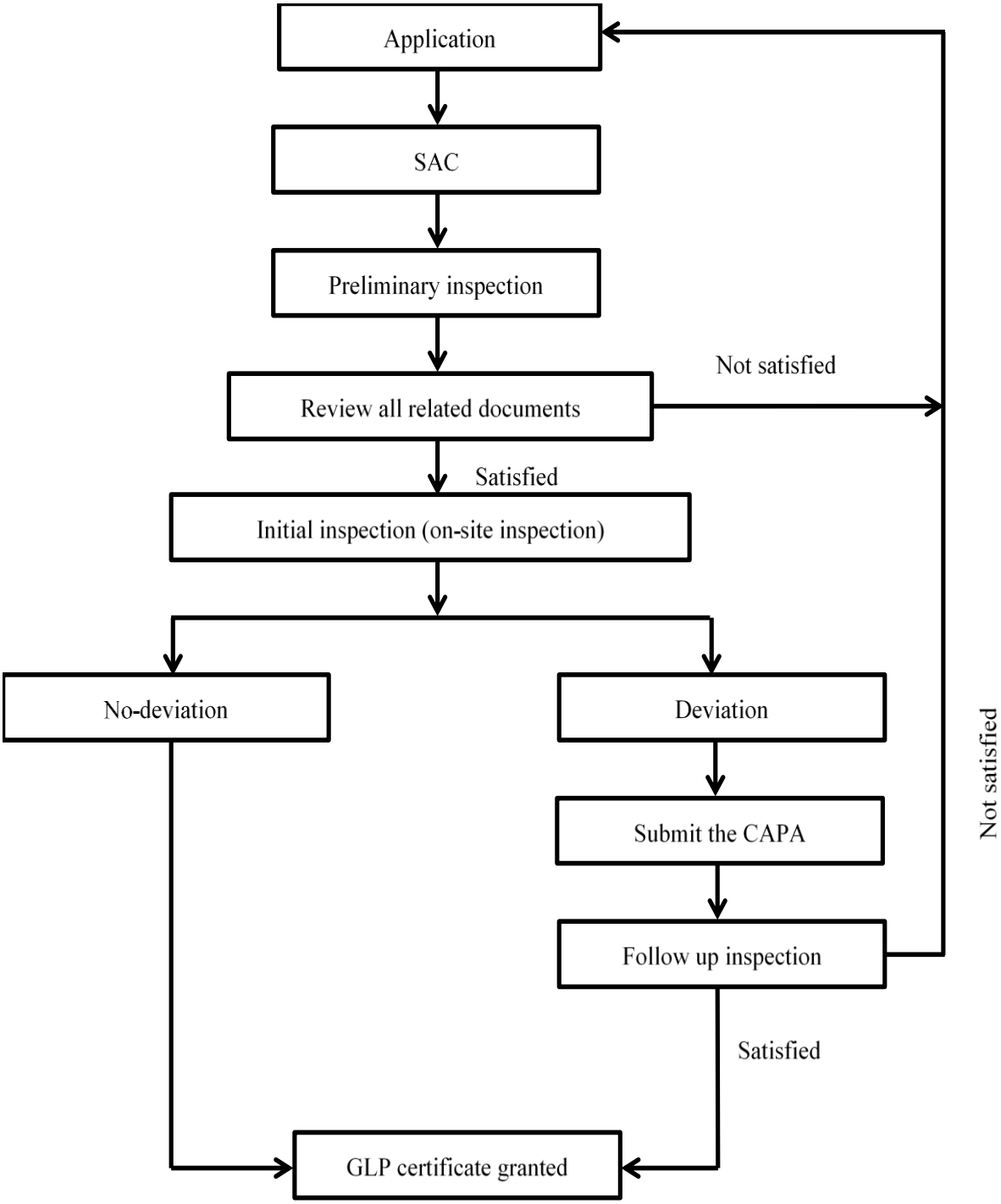

Figure 3: Inspections to grant a GLP certificate-Singapore

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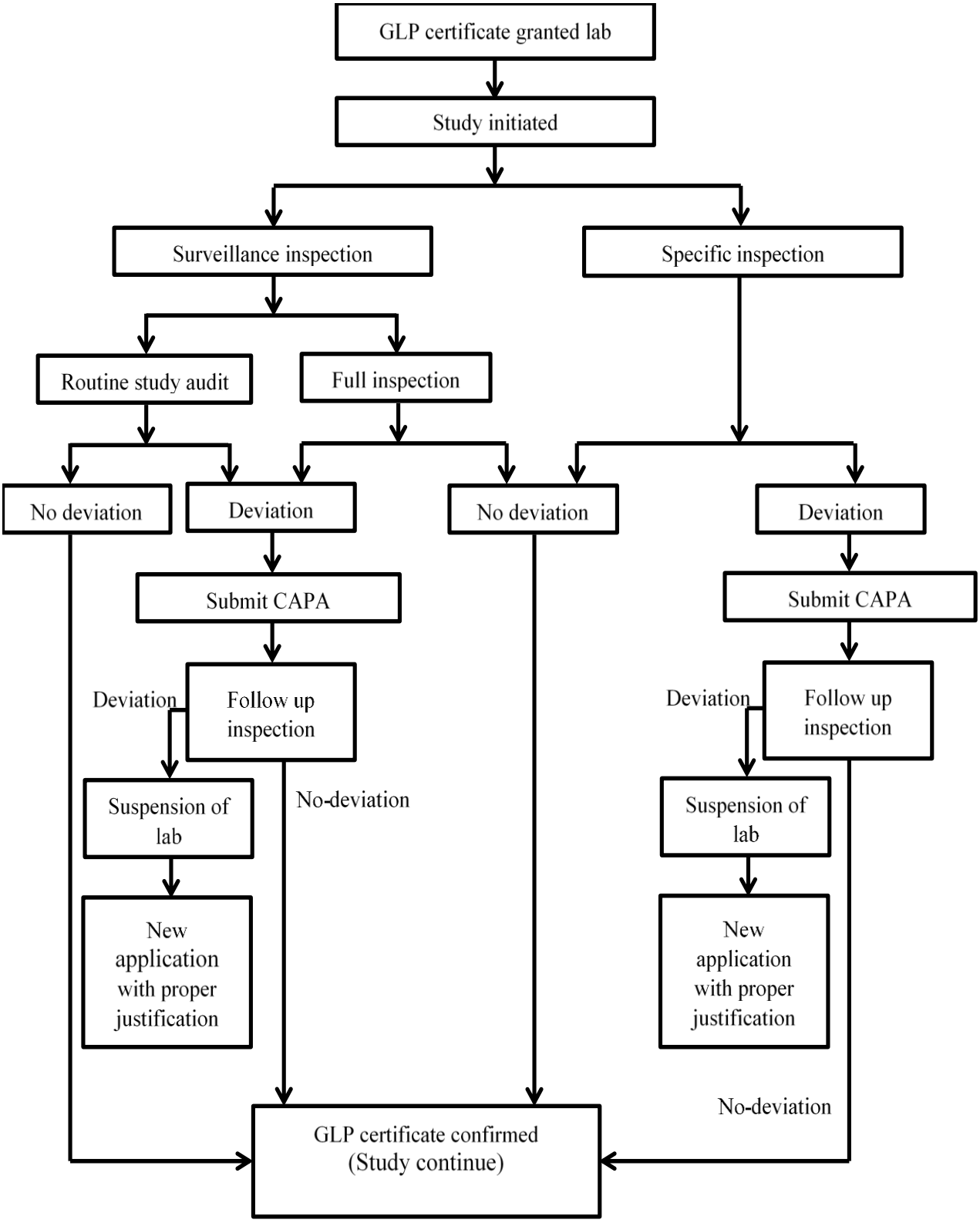

Figure 4: Inspections to confirm a GLP certificate (studies continue)-Singapore.

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10. Registration GLP. Compliance Programme

Table 4: Compilation of Good Laboratory Practice Compliance (Pre-Clinical study)

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

11. GLP01 - Procedures and Conditions for. 2014;(November):1–18. Available from: http:/Resources/sac_documents/Documents/Good Lab Practice/GLP 01 Procedures and Conditions for GLP Registration_Nov14.pdf