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BIOLOGICS IN INDIA: A BIRD VIEW

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ABSTRACT

A biological product is a substance that either contains or is derived from a living organism and is used for the prevention or cure of diseases. Biologic products may contain proteins that control the action of other proteins and cellular processes, genes that control production of vital proteins, modified human hormones, or cells that produce substances that suppress or activate components of the immune system. Biologic drugs are sometimes referred to as biologic response modifiers because they change the manner of operation of natural biologic intracellular and cellular actions. Biologics are significantly different from conventional medicines in that they contain

enormous, complex chemicals that are created utilizing genetically modified cells. Thus, each molecule of a biologic is unique. Our goal is to construct a step-by-step guide as to how to get crucial regulatory information for biologics throughout India that can be referred to as a reference. Have a system that will collect, analyze, document, disseminate, and maintain data for lifecycle management and regulatory compliance purposes.

Keywords: CDSCO, Biologics, DBT, GDP, GLP, GMP

INTRODUCTION:

Over the last three decades, biological medications have been utilized in clinical trials to treat diseases such as cancer, hepatitis, Multiple Sclerosis, and anemia.

According to the CDSCO, biologics are "drugs derived from living organisms or their derivatives for human use."

Cancer, rheumatoid arthritis, and a variety of other hazardous, debilitating, and life-threatening conditions are becoming increasingly reliant on them. Biologics are not the same as chemically synthesized medications. They are larger, more complex, and more variable, as they originate from live organisms [1].

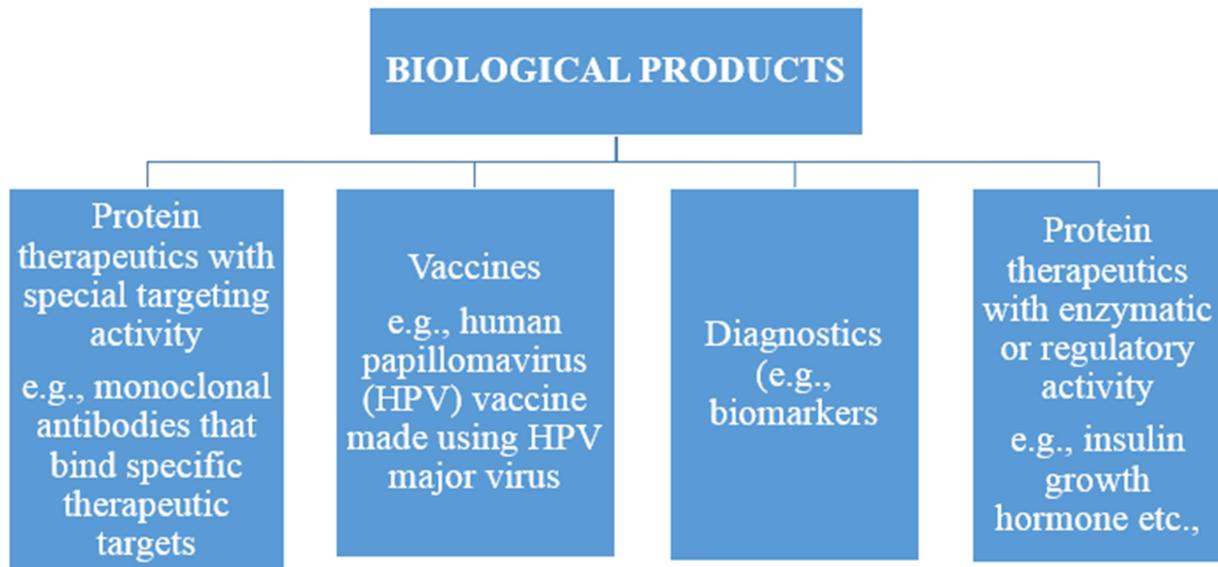
As biologics are proteins, they are rapidly digested and rendered inactive when taken orally. As a result, biologic drugs are

available in the form of infusion powders or injectable solutions.

"Guidelines on Biologics" prepared by CDSCO and Department of Biotechnology define the regulatory process for a Biologic to be commercialized in India. The CDSCO supervises and controls biologics. Many authorities examine and study biologics under CDSCO oversight.

Guidelines address biologics manufacturing, safety, effectiveness, and quality. Pre-market regulatory criteria include comparing quality preclinical and clinical studies. These instructions are designed to direct all stakeholders in ensuring compliance with the Drugs and Cosmetics Act 1940 and Rules as modified [2].

CLASSIFICATION OF BIOLOGICAL PRODUCT



APPLICABLE REGULATIONS

The following acts govern Biologics:

1. D and C act 1940
2. D and C rules 1945
3. Invasive microorganisms/Genetically modified organisms or cells rules notified under the Environment (Protection) Act 1986 for manufacturing, use, import, export and storage [3].

Additional criteria that apply are as follows:

1. Guidelines for the Safe Use of Recombinant DNA, 1990.
2. Preclinical and clinical data generation guidelines for rDNA vaccines, diagnostics, and other biologicals, 1999.

3. CDSCO Industry Guidance, 2008:

- Clinical Trial Application for Evaluating Safety and Efficacy
- Permission for New Drug Approval
- Post-approval modifications in biological products: Quality, Safety, and Efficacy Documents
- Preparation of High-Quality Data for New Drug Approval Submissions: Biotechnological/Biological Products

4. Guidelines and Handbook for Institutional Biosafety Committees (IBSCs), 2011.

5. Guidelines on Similar Biologics: Regulatory Requirements for marketing authorization in India 2012 [4].

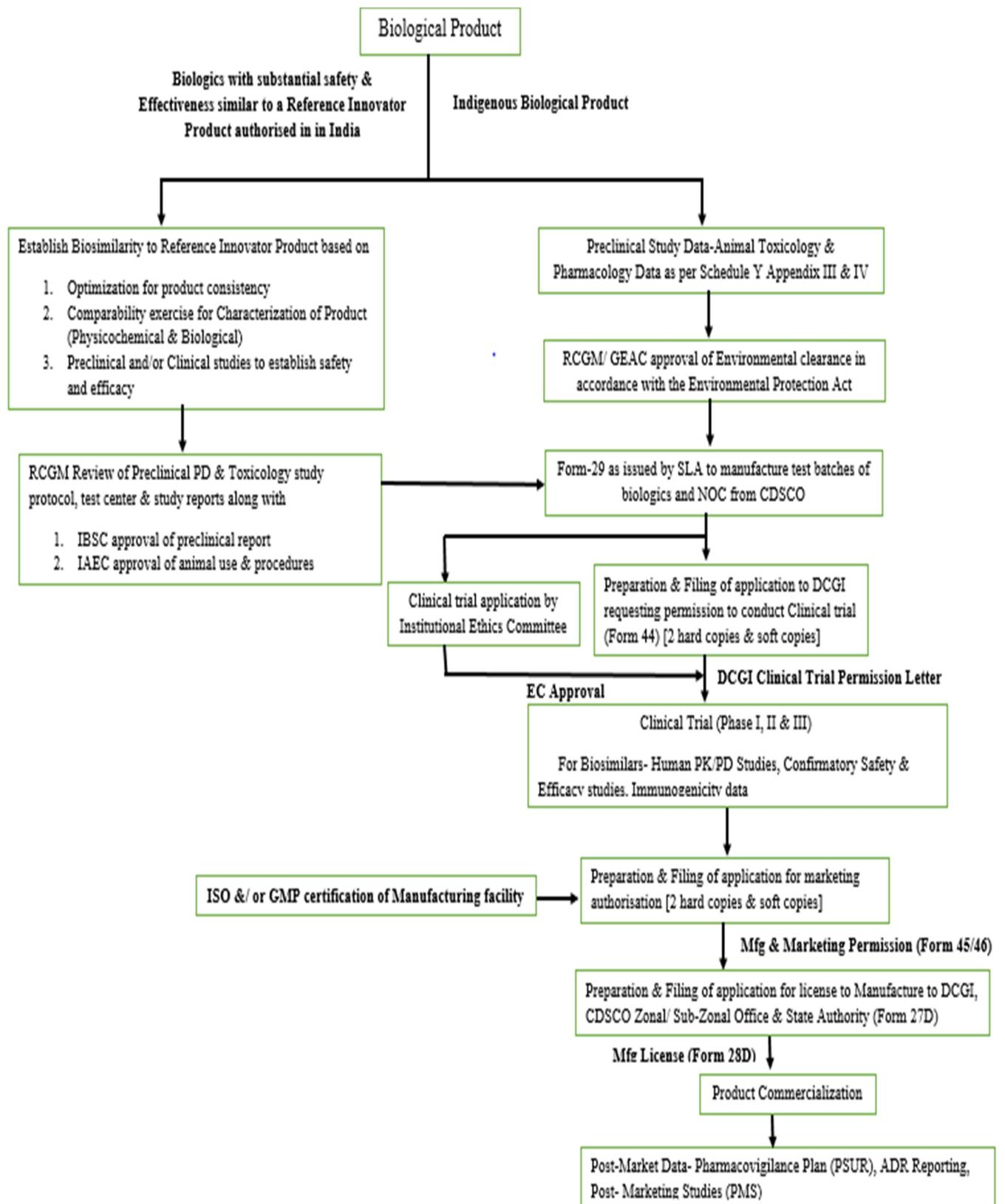


Figure 1: Regulatory Pathway for Biological Product

Approval required by offices and agencies:

- Biologics maker's research & Manufacturing facilities must be licensed by state authorities
- The federal Central Drugs Standard Control Organization (CDSCO) and the drugs controller general of India (DCGI), are responsible for reviewing preclinical and clinical trial applications and approving Biologic license applications. They also oversee the importation of drugs from other countries.

- In addition to the GEAC, RDAC, RCGM, and the IBSC, there are other committees at the state and district levels that oversee biosafety issues, as well as the State Biosafety Coordinating Committees (SBCC) and the Recombinant DNA Advisory Committee (RDAC) (DLC).

Types of Applications

Submissions of various applications forms to regulatory agencies are as follows: [5]

Purpose	Agency involvement	Application forms	Approval forms
License of manufacturing for examination, tests and analysis	CDSCO	Form no.30	Form no.29
Permission for preclinical studies	RCGM	Form no.C3	Form no.C4
Submission report of preclinical study	RCGM	Form no.C5	Form no.C6
Conduction of clinical trials	CDSCO	Form no.44	Letter of permission
Permission for manufacturing and marketing	CDSCO	Form no.44	Form no.45/46
License for import registration	CDSCO	Form no.40/8	Form no.41/10
License for manufacturing	CDSCO	Form no.27D	Form no.28D

DISCUSSION**FACTSHEET: Biologicals**

Table: Factsheet of NDA- Biologicals

REGULATORY FACTSHEET	
PRODUCT	Biologicals
COUNTRY	INDIA
TYPE OF APPLICATION	NDA
LIFECYCLE PHASE	MAA
REGULATORY DEPARTMENT	Ministry of Health and Family Welfare
REGULATORY AGENCY	Central Drug Standard and Control Organization(CDSCO)
REGULATORY CLASSIFICATION	Biologicals

- A quality system known as Good Laboratory Practice (GLP) is concerned with non-clinical health and environmental safety study planning, execution, monitoring, recording, archiving and reporting processes and circumstances.
- **Good Laboratory Practices certification is voluntary in nature.**
- Non-clinical safety testing of pharmaceutical, pesticide, cosmetic, veterinary medicine, food additive, feed additive, and industrial chemical products should follow GLP principles.
- Animal toxicology data as per Schedule Y has to be submitted
- In order to gather information on the characteristics and/or safety of these test items with regard to human health and/or the environment, they are being tested.
- GLP compliance ensures that registration authorities get truthful information about a product's safety.
- According to point 10 of Biologicals Checklist Manufacturing facilities data has to be submitted [6]
- It covers all phases of the product lifecycle, from the development of experimental medicines, to the transfer of technology, to the commercial manufacture of the final product.
- GMP is that part of quality management which ensures that products are consistently produced and controlled according to the quality standards appropriate to their intended use and as required by the marketing authorization, clinical trial authorization or product specification. GMP is concerned with both production and QC.

Accreditation & Accreditation body

No.	Accreditation	Accreditation Body	References
1.	GLP	NGCMA(National GLP Compliance Monitoring Authority)	http://indiaglp.gov.in/DocsNGCMA.htm
2.	GMP	State Licensing Authority	http://www.drugs.kar.nic.in/node/222.html

Table of Guidelines

No	Parameters	Section	References
1	GLP guidelines	OECD-GLP	http://www.oecd.org/chemicalsafety/testing/goodlaboratorypractice_glp.htm
2	GMP guidelines	WHO GMP	http://www.who.int/medicines/areas/quality_safety/quality_assurance/TRS986annex2.pdf
3	Schedule –M		http://www.cdsc.nic.in/writereaddata/ScheduleM(GMP)6.pdf
4	Schedule-Y		http://cdsc.nic.in/html/D&C_Rules_Schedule_Y.pdf

Table of Accreditation license:

No	Agency	Input	Output	Fees	Validity
1	NGCMA	GLP-102	GLP	25,000	3 years
2	CDSO	Application in the Form of Descriptive covering letter	GMP certificate	250	3 years

Documents required:

NGCMA-GLP:

No	Domain	Documents	Remarks
1	Administrative Information	<p>1.Types of application</p> <p>2. Details of Test Facility(TF)</p> <p>3. Details of Parent Organization</p>	<p>1. Application for certification, Re-Certification</p> <p>2.1 Name</p> <p>2.2 Address</p> <p>2.3 Fax.</p> <p>2.4 E-mail</p> <p>2.5 Phone No</p> <p>2.6 Contact person's name along with his details</p> <p>CRO <input type="text"/></p> <p>R and D Laboratory <input type="text"/></p> <p>University <input type="text"/></p> <p>Company/Organization <input type="text"/></p> <p>In addition to this (Please specify)</p> <p>3. (a) Is the TF-Stand-alone/Is it affiliated with the Parent organization?</p> <p>(b)If TF is part of parent organization, what choices are made by parent organization management?</p> <p>(c)(i)Name</p> <p>(ii)Address</p> <p>(iii) e-mail</p> <p>(iv)Fax</p> <p>(v) Phone no.</p> <p>(vi)Name of the contact person with contact details</p> <p>(vii)Legal status</p> <p>✓ Government organization</p>

		<p>4. Date of implementation of OECD in TF</p> <p>5. Sort of services offered by the facility</p> <p>6. Does TF perform Non-GLP testing and studies?</p> <p>7. Do GLP research involve additional test sites, subcontractors, or external scientists?</p> <p>8. Furnish documents</p> <p>9. Compose a master itinerary that</p>	<ul style="list-style-type: none"> ✓ Individual entrepreneurship ✓ Collaboration firm ✓ Trust ✓ Private corporation ✓ Public corporation <p>5. Chemical types: Industrial chemicals/Pharmaceuticals/ Pesticides /Veterinary Drugs/ /Cosmetic Products/ Feed Additives Food Additives/ Others(Specify) Subject Matter Expertise for which GLP compliance is desired Toxicity studies/Mutagenicity studies/Environmental toxicity studies/Residue studies/Analytical & Clinical Chemistry Testing 6.(a) Yes/No If yes, please describe the tests and relevant expertise. How often does it do non-GLP studies?</p> <p>8. (a) Recent organization charts including names of Personnel. (b) Information pertaining to the TF personnel as given below Name and designation Qualification with specialization Experience(Related to GLP) GLP training Details (c) Floor - plans with GLP marked area (d) Test Facility conducts and claims GLP compliance for toxicity research, information of animal house inspection/approval by CPCSEA (e) Approval/Clearance from office of DCGI for the tests involving use of Human tissue/Cells. (f) Details of biological testing systems. (g) List of instruments/equipment(s) including computerized systems. (h) List of Standard Operating Procedures (SOPs). (i) Documentation and preservation of SOPs. (j) Description of the Quality Assurance Unit's procedure. (k) Location of the archives giving details</p> <p>9.(i) GLP vs Non-GLP (ii) The study's title (iii) Test item/substance (iv) Name of study Director/PI/Test Site (v) Study initiation Date</p>
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		reflects all of the previous year's studies, both ongoing & completed.	(vi)Experiment Start & End Date (vii)Study Completion Date (viii)Archival date (ix)Remarks 10.(i)GLP vs Non GLP (ii)Study title (iii)Required test item (iv)Name & Address of the Regulatory Authority (v)Submission date (vi)Study status 11.(i)Name of Country & CMA (ii)Date of inspection (iii)Result (iv)Areas of Expertise 12.Work Timings/Weekly off Days
10.	Does your company submit studies directly or through a sponsor?		
11.	Provide the details of the GLP inspections of the TF conducted by any National/ foreign GLP compliance Monitoring Authority		
12.	Furnish Details.		
2	Quality Documents-CMC	NA	
3	Safety/Non-Clinical Documents	NA	
4	Efficacy/Clinical Document	NA	
5	Regulatory Approval	NA	
6	Quality certifications	NA	
7	Commercial and Marketing	NA	

SLA-GMP:

No	Domain	Documents	Required
1	Administrative Information	1.Application 2.Manufacturing License 3. certification for specific dosage forms 4. Tender notification 5. Fees-250/- 6. Format of Certificate 7. Copy of the power of attorney/authorization letter	1.Descriptive cover letter 2.Copy of valid manufacturing license has to be submitted 3. Copy/copies of product permission(Tablets, Capsules, Liquid Orals, Liquid Externals) 4.Applicable 5. Pay Order drawn in Favor of Drugs Controller for the State of Karnataka and its Xerox copy
2	Quality Documents-CMC	NA	

3	Safety/Non-Clinical Documents	NA	
4	Efficacy/Clinical Document	NA	
5	Regulatory Approval	NA	
6	Quality certifications	NA	
7	Commercial and Marketing	NA	

Approval Procedure GLP:

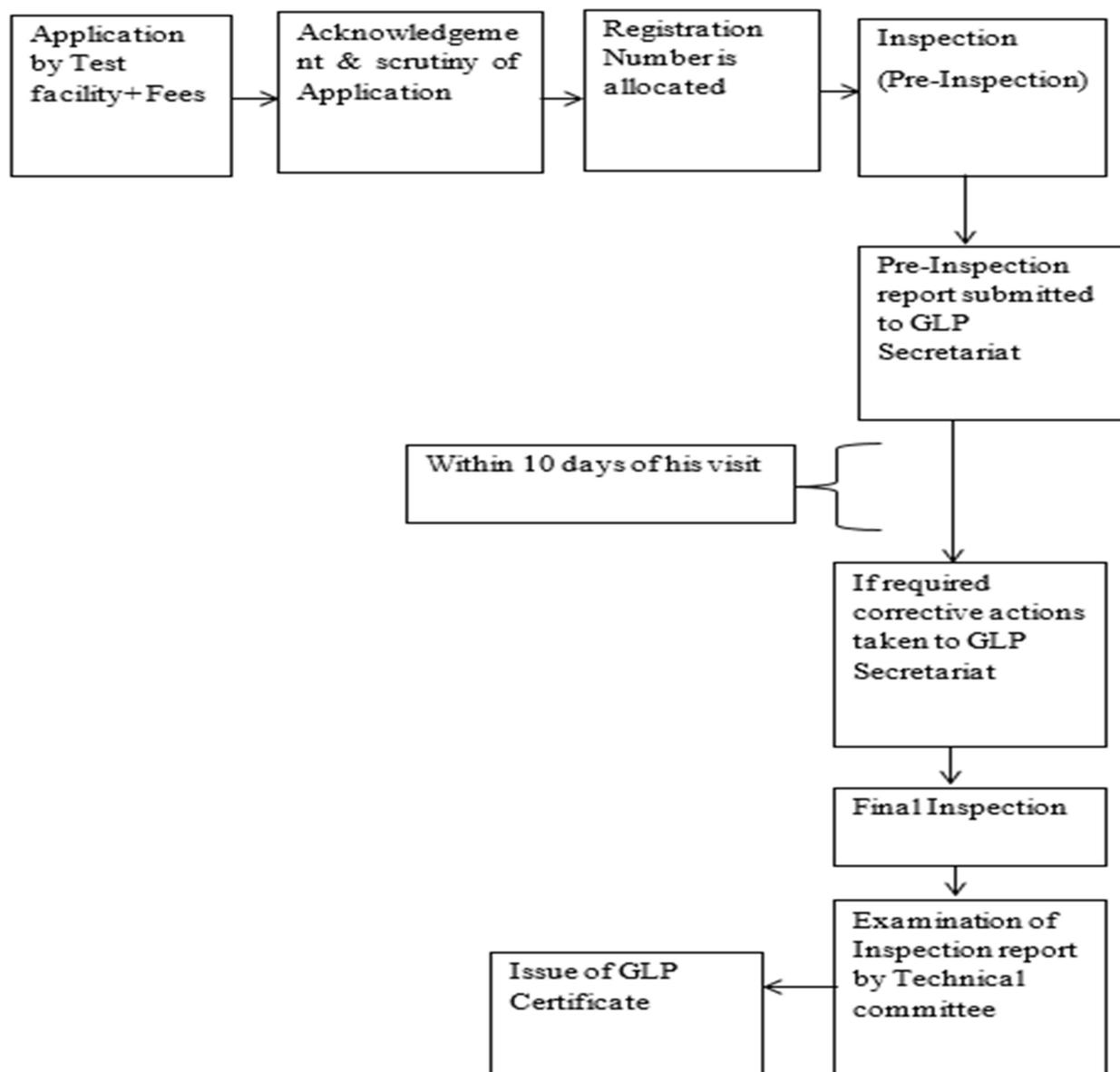


Figure 2: GLP Approval Process-Biologicals - India

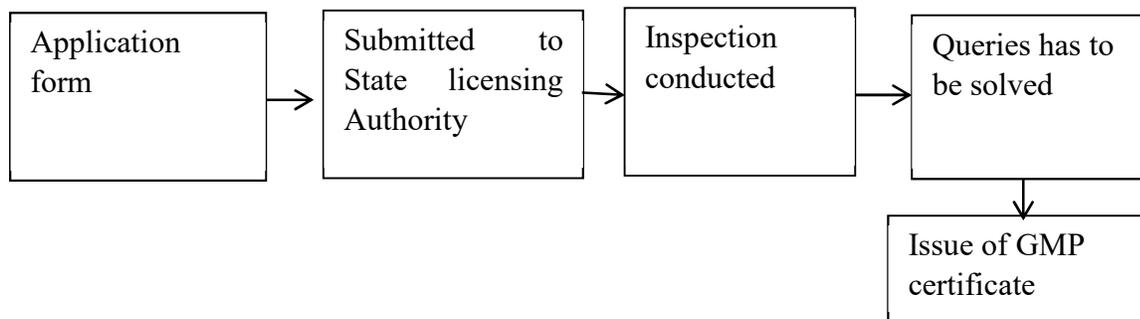
APPROVAL PROCEDURE GMP:

Figure 3: GMP Approval Process-Biologicals – India

GMP AUDIT CHECKLIST:

No	Particulars	Comments
1	Test facility organizations and personnel	
1.1	Test facility managements responsibilities	
1.2	Study director's Responsibilities	
1.3	Principal investigator's Responsibilities	
1.4	Study personnel's responsibilities	
2	Quality Assurance Programme	
2.1	General	
2.2	Responsibilities of the quality Assurance personnel	
3	Facilities	
3.1	Test system facilities	
3.2	Facilities for handling test and reference items	
3.3	Archive Facilities	
4	Apparatus ,Materials and reagents	
5	Test System	
5.1	Physical/Chemical	
5.2	Biological	
6	Test and Reference items	
6.1	Receipt, Handling, sampling and storage	
6.2	Characterizations	
7	Standard Operating Procedures	
8	Performance of study	
9	Reporting of study results	
10	Storage and retention of records and materials	

GMP INSPECTION CHECKLIST:

S. No.	Particulars	Y/N
1	Location and surroundings	
2	Building and premises	
3	Water system	
4	Disposal of waste	
5	Ware housing area	
6	Production area	
7	Ancillary area	
8	Quality control area	
9	Personnel	
10	Health, clothing and sanitation of workers	
11	Manufacturing operations and controls	
11.1	Sanitation in the manufacturing areas	
12	Raw materials	
13	Equipment	
14	Documentation and records	
15	Label and other printed Materials	
16	Quality Assurance	
17	Self-inspection and Quality audit	
18	Quality control system	
19	Specifications	
20	Master formula record	
21	Packaging records	
22	Batch processing records	
23	Standard operating procedures	
24	Product recalls	
25	Site master file	
26	Cleaning	
27	Media fill test	
28	Validation	
29	Air handling system	
30	Product information	

NGCMA-GLP:

The Department of Science & Technology (DST) created the National GLP Compliance Monitoring Authority (NGCMA) in India. Applicants must submit the required application fee as well as the necessary NGCMA form together with their completed NGCMA test facility/lab application. There is a laboratory pre-inspection by GLP inspectors, and then a final inspection is carried out. When the inspection team's

report is completed, it is reviewed by the Technical Committee, which then makes recommendations to the Chairman of the NGCMA. This decision is final. The validity of GLP Certification is for three years, during which time the GLP Secretariat arranges monitoring at 18 months after certification and a reassessment in the third year for the certification to be kept current [7].

SLA-GMP:

In India-CDSCO, State Licensing Authority of respective states will issue the GMP certificate.

CONCLUSION

Biologics are natural and very complex drugs used to treat various diseases and disorders. Nowadays Biotechnology also developing to manufacture different kinds of drugs like antibiotics, anticancer drugs. By this I came to know Biologics are classified as vaccines, serum, Blood & Blood products and rDNA products, Applicable regulations & regulatory pathways of biologics, Application forms that are required for the submission of the biological products, documents which are required for GLP submission and GMP submission and also procedures for the GLP and GMP.

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