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Recent Regulations and CDSCO Requirements for Registration of Biosimilars and Imports in India

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ABSTRACT

The main aim of this article was to study the various biosimilar product registration processes, regulations in imports, and requirements by the Indian Regulatory Authorities. The study emphasizes the challenges faced by stakeholders entering into the Indian market without difficulty by demonstration of strategy arrived from the established guidelines, regulations, and expert opinion. The study was undertaken to identify the challenges in biosimilar developments and evaluate the available guidelines and map the general requirements for registration including New Drugs and Clinical Trial Rules, 2019.

Keywords: Biosimilars, import, export, registration, New Drugs and Clinical Trial Rules, 2019

INTRODUCTION

A biosimilar is a biological product that is similar, but not identical, to a reference product, and therefore, requires separate market approval on patent expiration of the reference product. The original version of a biologic is referred to as the originator, innovator or reference drug and a biologic drug are also referred to as a biopharmaceutical, biologic or biological whereas Biosimilar is the term used in Europe and the US. Biopharmaceutical drugs comprise proteins derived from recombinant DNA technology and hybridoma technique including biological proteins (cytokines, hormones and clotting factors), monoclonal antibodies, vaccines, and cell and tissue-based therapies. In India, Central Drugs Standard Control Organization (CDSCO), the national regulatory authority evaluating the safety, efficacy and quality of drugs, defines Similar Biologic / biosimilar[6] as a product that is similar in terms of quality, safety and efficacy to an approved Reference Biologic product based on comparability. The Department of Biotechnology (DBT) through the Review Committee on Genetic Manipulation (RCGM)[6], oversees the development and preclinical evaluation of Similar Biologic in India. To overcome the challenge of reduced clinical research in India, CDSCO revisited the principles on clinical trials and new drugs and introduced new drugs and clinical trials rules, in 2019[13].

IMPORTANCE OF THE PROPOSED WORK

The main aim of this article was to study the biopharmaceutical products and biosimilar registration processes, regulations and requirements by the Indian regulatory authorities. The study emphasizes on the challenges faced by stakeholders entering the Indian market without difficulty by demonstration of strategy arrived from the established guidelines[12], regulations and expert opinion. The study was undertaken to identify the challenges in biosimilar developments[6] and imports and evaluate the available guidelines and map the general requirements for registration.

The manufacturing processes leading to the production of biotechnological medicines are more complex. For products without Live Micro-organisms (LMO), RCGM & DCGI approval is mandatory for Indigenous Product Development[6], Manufacturing & Marketing whereas for Import and Marketing, DCGI approval is required. Whereas products with LMO are evaluated by RCGM, GEAC & DCGI for Indigenous product development, Manufacturing & Marketing and Import of bulk, for manufacturing & marketing.

For Import & Marketing, GEAC & DCGI permission is required. Biological products are considered as New Drugs as per the Indian Drugs and Cosmetics Act1. Products intended to be marketed in India are regulated by either the Drugs Controller General of India (DCGI) and the Department of

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Biotechnology (DBT). The history of regulatory related to drug import, manufacture and sale are covered under the Drugs and Cosmetics Act of 1940 and the Drugs and Cosmetics Rules of 1945. The Act's main objective is to ensure that available human drugs are safe efficacious and conform to prescribed quality standards and marketed products are safe for use.

HIGHLIGHTS IN THE NEW DRUGS AND CLINICAL TRIALS RULES, 2019

Ministry of Health and Family Welfare [MoHFW], India, has notified the "New Drugs and Clinical Trials Rules, 2019" on 25th March 2019 vide Gazette Notification G.S.R 227(E) dated 19.03.2019. These rules will apply to all new drugs, investigational new drugs for human use, clinical trial, bioequivalence study, bioavailability study and Ethics Committee. The new rules will supersede Part XA and Schedule Y of the Drugs and Cosmetics Rules, with immediate effect. If there is any inconsistency between these rules and any other rule made under the Drugs & Cosmetics Act, the provisions of these rules shall prevail over such other rules. Actions taken according to the existing rules [Drugs & Cosmetics Rules, 1945] shall continue to be in effect and valid. This means existing licenses, orders; directions will continue to remain valid. The new rules aim to promote clinical research in India by providing for a predictable, transparent and effective regulation for clinical trials and by ensuring faster accessibility of new drugs to the Indian population. The requirement of a local clinical trial may be waived for approval of a new drug if it is approved and marketed in any of the countries specified by the Drugs Controller General with the approval of the government.

REQUIREMENTS FOR REGISTRATION OF A BIOLOGICAL DRUG

(i) Application in Form 40

(ii) Challan fees of 10000 USD for registration of manufacturing site of foreign manufacturer and 5000 USD for single drug and 5000 USD each for an additional drug.

(iii) Power of Attorney; sign/stamp of both foreign manufacturer and authorized agent in India; Apostilled or Notarized by Indian Embassy in country of origin.3

(iv) Import permission on Form CT-23 (Formulation) and / or Form CT-22 (Bulk).

(v) Notarized copy of Wholesale/ Manufacturing License.

(vi) Schedule D (I) & Schedule D (II) Sign, Date, Stamp by the overseas manufacturer.

(vii) Plant Master File (PMF) / Site Master File (SMF), Notarised in a foreign country.

(viii) GMP certificate, Notarised in the country of origin.

(ix) Certificate of Pharmaceutical Products (COPP), Notarised in the country of origin

(x) Regulatory status of the drug in the country of origin including registration, launching, and withdrawal status.

(xi) Free Sale Certificate (FSC); Notarized in country of origin.

(xii) Drug Master File (DMF); Notarized in country of origin.

(xiii) Annexures A / C of Schedule D (II)

Annexure A: For Blood products.

Annexure C: For rDNA product and Vaccines.

(xiv) List of countries where Marketing Authorization is granted

(xv) List of countries where the drug is patented

(xvi) Certificate of analysis and Stability data for five batches.

(xvii) Original Label, Carton and Package insert.

(xviii) Details of the safety handling procedure of the drug

(xix) Post Marketing Surveillance reports

(xx) Pharmacological and Toxicology information

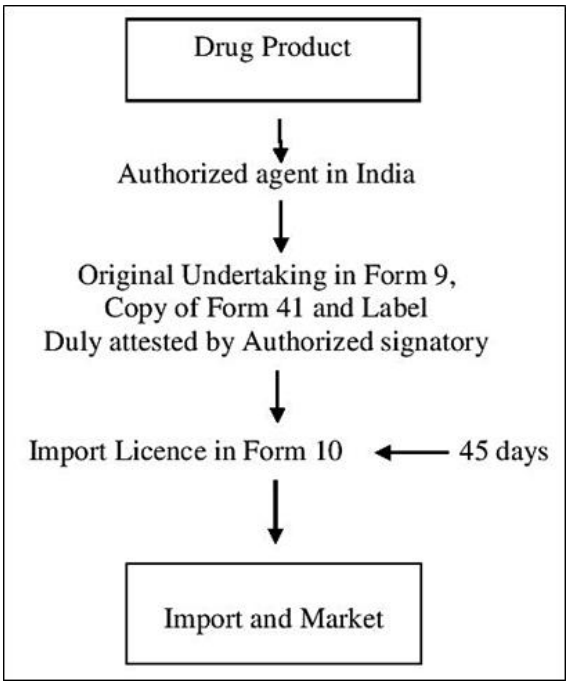

Fig. 1: Regulatory Pathway for Import and Marketing of Drug without Registration in India

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Summary of the changes brought in by the New Drugs & Clinical Trials Rules, 2019[12]

A comparison with previous regulatory requirements is presented in tabular form

Rule / Subject	New requirement	Previous requirement
Definitions – modified definitions	'New drug' definition has been modified. Modified & Sustained release form of a drug or novel drug delivery system of any drug approved previously, will always be deemed to be new drugs, even after 4 years of initial approval	Modified & Sustained release formulations were not considered new drugs after 4 years from the time of initial approval
Authorities & Officers Delegation of powers of CLA	The Drugs Controller, India, with the prior approval of the Central Government, may, by an order in writing, delegate all or any of powers of the Central Licencing Authority to any other officer of the Central Drugs Standard Control Organisation not below the rank of Assistant Drugs Controller (India). [Rule 4]	The licensing authority may with the approval of the Central Government by an order in writing delegate the power to sign licences and Registration Certificates and such other powers as may be specified in the order to any other person under his control. [Rule 22]
Ethics Committee for BA, BE studies Approval timeline Validity of registration Conditions of registration	45 working days from the date of receipt of the application 5 years Any change in the membership or the constitution of the registered Ethics Committee shall be intimated in writing to the Central Licencing Authority within thirty working days.	100 days approval time considered 3 years The Licensing Authority shall be informed in writing in case of any change in the membership or the constitution of the Ethics Committee takes place.
Bioavailability and Bioequivalence Study of New Drugs and Investigational New Drugs	Application to be submitted in Form CT 05 Permission granted in Form CT 07 Approval timeline – 90 working days	Application to be submitted in Form 44 Permission granted as an approval letter, not in any specific format. Approval timeline – 45 days
Rule / Subject	**New requirement**	**Previous requirement**
Validity of permission	Application to be submitted in Form CT 05 Permission granted in Form CT 07 Approval timeline – 90 working days The permission to conduct a bioavailability or bioequivalence study granted under rule 34 in Form CT-07 shall remain valid for a period of one year from the date of its issue unless suspended or canceled by the Central Licencing Authority. •In exceptional circumstances, where the Central Licencing Authority is satisfied about the necessity for an extension beyond one year, the said authority may, on the request of the applicant made in writing, extend the period of permission granted for a further period of one year. • study shall be initiated by	Application to be submitted in Form 44 Permission is granted as approval letter, not in any specific format. Approval timeline – 45 days No such requirement previously.

	enrolling the first subject within a period of one year from the date of grant of permission, failing which prior permission from the Central Licencing Authority shall be required.	
Manufacture of new drugs or IND for CT, BA, BE or for Examination Test and analysis Approval process Approval validity Manufacturing	Application to be submitted in Form CT-10 Approval to be granted in Form CT-11 Approval timeline – 90 working days The permission will remain valid for 3 years, An extension of 1 year may be granted Manufacturing of drugs shall be in accordance with the principles of Good Manufacturing Practices	No specific format is prescribed for application or approval [NOC for Form 29] Approval timelines – 60 days No validity defined for Form 29 NOC This was not explicitly defined earlier.

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Rule / Subject	New requirement	Previous requirement
Import of new drugs and IND for CT, BA, BE or for Examination Test and analysis Approval process Validity of license Conditions of license	Application to be submitted in CT-16 Approval to be granted in CT-17 Approval timeline – 90 days The licence will remain valid for 3 years An extension of 1 year may be granted Licensee to ensure that the drug has been manufactured following the principles of Good Manufacturing Practices;	Application submitted in Form 12 Approval granted in Form 11 Approval timeline – 45 days 3 years No provision of an extension. New license may be obtained instead. This was not explicitly defined earlier.
Import of new drugs for sale or distribution Permission to import a new drug	Application to be submitted in CT-18 Approval to be granted in CT-19 [API] or CT-20 [Finished formulation] Approval timeline – 90 working days Conditions for waiver of local clinical trials are defined very clearly in the new regulations.	Application submitted in Form 44 Approval granted in Form 45 [Finished formulation] or Form 45A [API] Approval timeline –180 days Local clinical trials may not be necessary if the drug is of such a nature that the Licensing Authority may, in public interest, decide to grant such permission based on data available from other countries.
Manufacture of new drugs for sale or for distribution Permission to manufacture a new drug	Application to be submitted in CT-21 Approval to be granted in CT-22 [API] or CT-22 [Finished formulation]	Application submitted in Form 44 Approval granted in Form 46 [Finished formulation] or Form 46A [API]
	Approval timeline – 90 working days Conditions for waiver of local clinical trials are defined very clearly in the new regulations.	Approval timeline –180 days Local clinical trials may not be necessary if the drug is of such nature that the Licensing Authority in Rule 21 may, in the public interest, decide to grant such permission based on data available from other countries

Rule / Subject	New requirement	Previous requirement
Amendments of Drugs and Cosmetics Rules, 1945	In the Drugs and Cosmetics Rules 1945, after rule 122DA the following new rule shall be inserted, namely: "122DAA. Non-application of certain rules for new drugs and investigational new drugs for human use. Part XA and Schedule Y shall not be applicable in respect of new drugs and investigational new drugs for human use from the date of coming into force of the New Drugs and Clinical Trials Rules, 2019, and the references in respect of human use made in these rules shall respectively be omitted, and the construction thereof shall be construed accordingly and shall stand amended with all cogent	Not applicable

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	meaning of the grammar".	
Stability data requirements for new drug substances and formulations intended to be stored under general conditions Stability data requirements for drug substances and formulations intended to be stored in a refrigerator	Long term – 30°C ±2°C/75% RH ±5% RH – 6 or 12 months Accelerated - 40°C ±2°C/75% RH ±5% RH - 6 months Long term - 5°C ±3°C – 6 or 12 months Accelerated - 25°C ±2°C/60% RH ±5% RH - 6 months	Long term – 30°C ±2°C/65% RH ±5% RH -12 months Accelerated - 40°C ±2°C/75% RH ±5% RH - 6 months Long term - 5°C ±3°C -12 months Accelerated - 25°C ±2°C/60% RH ±5% RH - 6 months
Stability data requirements for drug substances and formulations intended to be stored in a freezer	Long term - 5°C ±3°C – 6 or 12 months	Long term - 5°C ±3°C 12 months
Requirements and guidelines for the conduct of BA BE study of new drugs of investigational new drugs	The requirements of BA BE studies are explicitly prescribed under Fourth Schedule of the Rules.	The requirements of BA BE studies are not explicitly prescribed
Rule / Subject	**New requirement**	**Previous requirement**
	Clearly defined process for; • General principles • BA BE study center • Organisation and management • Documented SOPs • Clinical Pharmacological Unit • Maintenance of records • Retention of samples	
Revision in application fees for various licenses: Permission to import new drug (Finished Formulation or API) for marketing Permission to import new drug (Finished Formulation or API) already approved for marketing Reconsideration of application for permission to import the new drug for marketing Application for permission to import approved new drug for new claims, new indication or new dosage form or new route of administration or new strength for marketing Application for permission to manufacture new drug (Finished Formulation or Active Pharmaceutical Ingredient) for sale or Distribution Application for permission to manufacture new drug (Finished formulation or Active Pharmaceutical Ingredient) already approved in the country for sale or distribution Application for permission to manufacture approved new drug for new claims, new indication or new dosage form	5,00,000 INR	2,50,000 INR 1,00,000 INR 2,00,000 INR 50,000 INR 300,000 INR 500,000 INR 200,000 INR 300,000 INR 500,000 INR
		No fees 100,000 INR 50,000 INR 50,000 INR or 15,000 INR 15,000 INR 50,000 INR

or new route of administration or new strength for sale or distribution Application for permission to manufacture fixed dose combination having one or more of the ingredients as unapproved new molecules for sale or distribution		

CONCLUSION

Clinical trials and the New Drug approval process are considered as the key tools in new drug evaluation. Overall, the new rules will further benefit patients and industry but are comprehensive, well balanced and will likely improve the ethical and quality standards of clinical trials in the country. To speed up the clinical trial process and to encourage drug development, the approval for clinical trials in 30 working days for locals drugs. Provision for accelerated product approval under some conditions, together with the provision of pre and post-submission meetings with the CDSCO office, would add certainty and confidence within the system.

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