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Recent regulation, challenges in regulatory requirement and approval procedure of biological in India, US & Europe

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Abstract
The current constraints on Regulatory Affairs show that various nations have distinct regulatory requirements that must be met to receive approval for new pharmaceuticals via the Marketing Authorization Application (MAA). Each nation has its own regulatory body that is responsible for enforcing existing laws and formulating new ones to manage the pharmaceutical industry. The regulatory body is responsible for enforcing this duty. After a lead therapeutic molecule has been identified, more research must be done outside of a clinical setting to demonstrate the treatment is both effective and safe before it can advance into human trials. Once an application has been submitted to the appropriate body in the country of interest, clinical trials can begin. Each of the three phases of the ongoing clinical studies strictly follows the protocol. An application must be filed with the relevant authorities before the substance may be sold legally. The application is sent to the relevant bodies for examination, and approval is granted if it is determined that the drug meets the necessary standards of quality, safety, and efficacy.

Keywords: Clinical, regulatory, drugs

Introduction
The regulatory requirements that must be completed for a novel pharmaceutical to be licensed now vary greatly from one nation to the next. The Marketing Authorization Application, or MAA, cannot use a single regulatory strategy that works in several countries. Therefore, it is crucial to be familiar with the MAA regulations in effect in each country. Novel medicines must first meet the regulatory requirements of the target country before they may be legally sold there. The specifics of this rule are different in each country. To get a novel pharmaceutical approved, it's difficult to adopt a cohesive regulatory approach across several countries. Therefore, it is important to learn about the regulatory challenges that exist in different countries. It is well-known that the pharmaceutical markets in the United States of America (USA) and the European Union (EU) are among the most promising in the world; consequently, many companies place a special emphasis on the pharmaceutical regulations of these two areas. As a result, this article explores India's regulatory strategies. When a promising lead molecule against a certain disease has been identified, the next step is optimization. After a drug has been created, the next stage is to conduct tests on animals to ensure its safety and efficacy. The NDA undergoes a technical review once it has been received by the agency. This check ensures that all required details have been included in the application, making "filing" possible. Through this analysis, we can see if all requested information and data have been provided. There are three potential next steps that might be communicated to the sponsor following the conclusion of an NDA review.
The biggest market for biosimilars is Europe, followed by Asia and the Pacific; however, it is expected that the economies of China and India would grow the quickest. It is projected that Brazil will also see rapid economic expansion during the next five years. The European Union (EU) released its first opinion on biosimilars in the early 2000s, and since then, it has issued and regularly revised several recommendations pertaining to individual biosimilars. These standards will also be reviewed often. Around the same time, the United States Food and Drug Administration (FDA) began debating the issue of so-called "follow-on biologics,"

releasing a first draughts of its guidance in February 2012 and revising it in 2015. India, China, and Brazil did not release their biosimilar guidelines until 2010, 2012, and 2015, respectively. Proteins are more intricate than simple chemicals since there is no one, universally repeated structure for them. In contrast, it is extremely unlikely that a protein will have the same structure as a standard product.

The protein structure can change in a wide variety of ways. Even apparently little structural alterations, such as variations in glycosylation patterns, can have a significant influence on the safety and efficacy of a protein, making it crucial to evaluate these differences. Since biosimilars are not "generic medicines," the typical steps associated with authorizing them do not apply to them. Producing biosimilars is a complex and expensive procedure since it requires specialist knowledge to develop the right cell clone that can generate the protein. The current method of analysis may be inadequate for spotting all the relevant structural and functional differences between two protein products. It's also possible that our understanding of how a product's structural properties influence its medicinal efficacy is limited. Studies of bioavailability and bioequivalence cannot be relied upon to determine bio similarity due to the complexity of biotechnology-derived goods. To determine whether two compounds are biosimilar, we need evidence from analytical tests, animal experiments, and human clinical trials.

Clinical and regulatory experiences, such as the availability of sensitive clinical endpoints and model conditions, the current state of the art of analytical procedures, and the manufacturing processes that are used all play a role in determining whether the "biosimilar" approach would be applicable to a specific biological medicinal product. The approach's applicability hinges on these considerations. The biosimilar should have the same dosage mechanism and administration route as the reference pharmaceutical product. Deviations from the reference product, whether in formulation or in the list of components, must be explained or further investigation conducted.

U.S. Approval and submission process for regulators

Methods Used by the FDA in Approval of Medications and Biological Products9 In 1820, a new era in the oversight of medicines in the United States began with the publication of the United States Pharmacopoeia. The first Food and Drugs Act was created by Congress in 1906. It required that all drugs meet certain safety and efficacy standards set by the government. However, the Federal Food, Drug, and Cosmetic Act (of 1938) introduced further criteria saying that new medications must first demonstrate that they are safe before being put on the market, in reaction to the sulphadiazine crisis that happened in 1937. Additionally, in 1962, the Kefauver-Harris Amendment law was passed. Pharmaceutical businesses are required by law to demonstrate the safety and efficacy of their medication before it can be sold to the public. The Food and Drug Administration is responsible for maintaining and enhancing public health and safety. The FDA's new medication approval procedure consists of two phases: clinical trials (CT) and NDA clearance. These steps are quite like those in the standard procedure for approving new medications. The approval procedure for an experimental new drug (IND) cannot begin until an IND application has been filed to the FDA. High-quality preclinical data must be included in the IND application to show that human testing of the treatment is necessary. Clinical testing is performed on about 85% of drugs, and then an IND application is submitted. The next step is to perform clinical studies, which will fall into one of three phases. An NDA, or new drug application, cannot be filed until all three phases of clinical testing have been completed, and all necessary information regarding the drug's safety and efficacy in both humans and animals, as well as the drug's intended labelling, manufacturing, and pharmacokinetics, has been provided. Preclinical and clinical investigations, as well as a risk-benefit analysis (to see if the benefits of the product exceed the risks), are reviewed by experts at the Centre for Drug Evaluation and Research. Approval of an NDA is typically granted within two years, while this process might take as little as two months or as long as several years.

How to get approval from and submit to India regulators

The Indian parliament passed the Drug and Cosmetic Act in 1940 and the Drug and Cosmetic Rules in 1945 to regulate the commercialization of pharmaceuticals and cosmetics in the country. Drugs Controller General of India (DCGI) and the Central Drugs Standard Control Organization (CDSCO) were established. When it was created in 1988, Schedule Y was included to India's Drug and Cosmetics Rules 1945. Schedule Y, which outlines the regulations and methods for conducting clinical trials, was updated in 2005 to bring it in line with internationally accepted protocol. Some of the changes that will occur because of these modifications include the establishment of definitions for Phase I-IV studies and the specific responsibilities for investigators and sponsors31. Separate groups were created for the clinical studies in 2006. Category A countries are those with competent and mature regulatory frameworks that allow clinical trials to be conducted there. Category B, on the other hand, includes all the other clinical trials. In addition to the letter A. Fast tracking is available in India for category A clinical trials that have received approval in the United States, the United Kingdom, Switzerland, Australia, Canada, Germany, South Africa, Japan, and the European Union. Approval for category B clinical research normally takes 16-18 weeks32 because to the additional scrutiny they get. An application including chemical, manufacturing, quality control, and animal testing data must be submitted to DCGI to take part in clinical trials in India.

Include the most up-to-date version of the investigator's brochures, the research protocol, and any other relevant paperwork for informed consent, along with the current date. A copy of the application must be submitted to the ethics review board, and clinical studies cannot begin without first gaining approval from the DCGI. To determine the safest dose for human administration and to identify any potential side effects, phase I clinical trials are conducted on healthy human volunteers. Ten to twelve subjects at each of 32 dose levels are used in phase II clinical investigations to determine the drug's therapeutic utility and optimal dosing range. At least one hundred patients (across three to four sites) must participate in confirmatory trials (Phase III) to provide data on the treatment's efficacy and safety, which is crucial for validating efficacy and safety claims. If the innovative pharmaceutical has not been approved for sale in any other country, Phase III trials involving at least 500 patients should be conducted at a minimum of 10 locations.

Application for novel pharmaceutical registration (using form 44 and comprehensive information regarding preclinical and clinical testing) is filed when clinical trials are finished. Information on the medicine's efficacy and feasibility, as well as the drug's current marketing status in other countries, must be supplied.

Filing a Request for Promotional Release

The regulatory requirements that must be completed for a novel pharmaceutical to be licensed now vary greatly from one nation to the next. When seeking to apply for marketing authorization (MAA) in many countries, it is very hard to find a single regulatory strategy that works across the board. Therefore, it is crucial to be familiar with the MAA regulations that apply in each country. The primary feedback and control system is depicted in Figure 2.

Drug Approval in the USA (Parts 1-3)

The standards for the licensing of new drugs in the United States of America may be the most stringent in the world. There is a common belief that the United States has the strictest standards for medication approval in the world.

Application for New Investigational Drug; often known as an IND

This is a request to start human testing of the medication in clinical settings once the FDA has determined that it is safe to do so based on the results of the medication's preclinical research. A business or organization, known as a "Sponsor," is responsible for submitting the IND application. A pre-IND conference can be arranged with the FDA to discuss a wide range of potential issues.

First, data for clinical studies cannot be gathered without first organizing animal research.

Second, the plan for how the clinical study will be executed.

3. The experimental drug's composition, production, and quality control

The Sponsor will benefit from this meeting since it will help them organize animal studies, collect data, and create a clinical procedure that follows FDA guidelines. In Figure 1, we have provided a simple flowchart of the IND process for your review.

(NDA) is shorthand for "new drug application

Once clinical studies show that a new drug is generally safe and effective and will not place patients in danger due to risks that are unreasonably high, the manufacturer submits the New Medicine Application (NDA), which is the actual request to manufacture and sell the medicine in the United States. See Figure 3 for an illustration of the NDA process.

The abbreviation "ANDA" refers to an "abbreviated new drug application."

The submission is a request for generic medication approval. The sponsor is not required to repeat the clinical testing that were performed on the original version of the product that had the brand name. Instead, manufacturers of generic drugs must show that their product is bioequivalent to an already-approved brand-name drug.

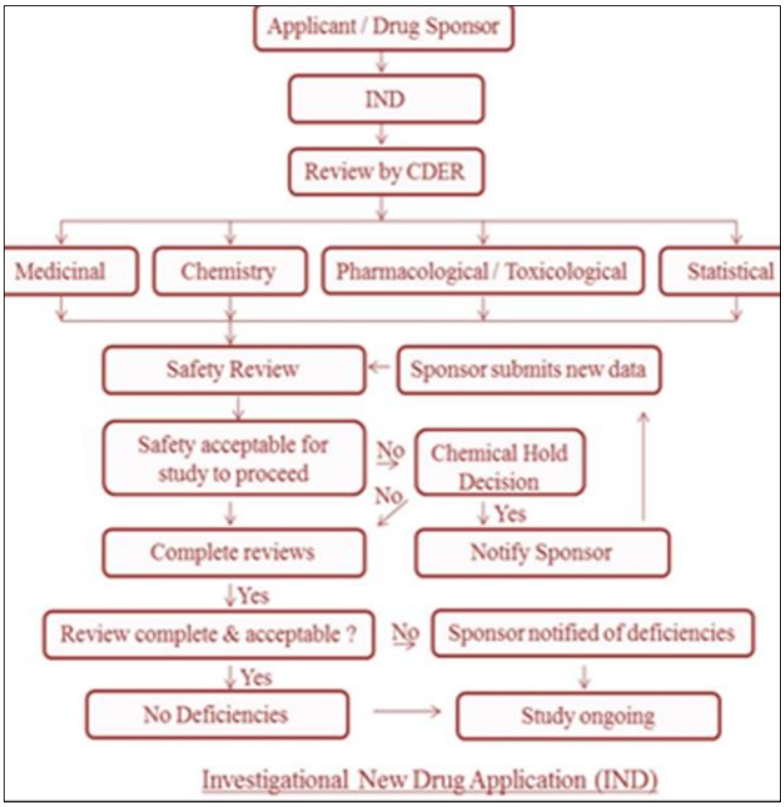

Fig 1: Flowchart for an INDA, or an investigational new drug application

Acceptance of Drugs in Europe (4-6)

A drug must meet the same standards as those in the United States before it can gain regulatory clearance to be marketed in the market in the European Union. First, you'll need to apply for a clinical trial, and then you'll need to apply for marketing approval. Research in Humans Until July 2013, applications for marketing authorization were only granted at the member state level, but since then, they have been authorized both at the member state and central levels. The European Union has expanded to include 28 countries.

Technique Where Authority Is Based in One Place

A marketing authorization that is valid throughout the European Union can be obtained through a centralized approach. This is a method that has been documented elsewhere.

Therefore, a single authorization is sufficient for travel across the European Union (EU), Norway, Iceland, and Liechtenstein.

The Rapporteur oversees determining the merits of each application submitted.

Timeline: The EMA's recommendation will be forwarded to the European Commission for final approval within 210 days.

Any drug created via the use of biotechnology, including but not limited to genetic engineering, must follow a standardized protocol.

Medications used to treat conditions including cancer, HIV/AIDS, diabetes, neurological problems, autoimmune diseases, and other immunological dysfunctions.

Meds given the official moniker "Orphan medicines" because of their limited use to rare diseases.

Books to read for review

Author Philip Home's 2015 tome with the insulin analogue patent soon to expire, it is likely that several imitation biopharmaceutical products will be submitted for approval. Researchers have concluded that strict control and considerable caution are necessary when using biosimilars in any therapeutic field. Recommendations provided by regulatory agencies across the world on the licensing of biosimilars, including insulin biosimilars, were reviewed. The data was collected via online search and subsequent use of the specified cross-referencing guidelines.

An enormous amount of study in chemistry, manufacturing, quality control, preclinical science, and clinical testing is required for the creation of a new pharmaceutical. Drug reviewers that work for regulatory bodies throughout the world are responsible for deciding whether the study findings support the safety, effectiveness, and quality control of a new drug product to serve the public health. The marketing of medicines is governed by laws and regulations, and they are enforced and supplemented by recommendations issued by regulatory authorities in each country. This article compares the processes for approving new pharmaceuticals in the United States of America, Europe, and India.

A.B. Aghade. Both the federal government and individual states in India are involved in the process of regulating pharmaceutical items. The major authority in the nation charged for vetting pharmaceuticals for public use is the Central Drugs Standards Control Organization (CDSCO). The goal of this study is to offer a brief introduction and overview of the regulatory procedure that is followed in India for the approval of new medications by providing examples of applications for INDs and NDAs. In addition, this page includes details and information about the procedure and documentation required to apply for new medications in India.

The reason for this study

1. One goal is to study the steps involved in getting products through U.S. regulations.
2. investigate the Mutual Recognition Procedure for Marketing Authorization Applications

An applicant can apply for a marketing authorization in a CMS other than the RMS (the state where the drug was first licensed) by way of the Mutual Recognition method.

The applicant must submit the same dossier to all EU member states where marketing approval is sought. All pertinent details should be included in this dossier. When one member state (the "RMS") decides to conduct the examination of the medical product, it immediately notifies the other member states (the "CMS") to which applications have previously been filed.

One, RMS will share its findings with other states and offer opinion on them.

Second, the main end-user of this type of drug approval process is the generic pharmaceutical industry.

Third, this procedure might take as long as 390 days.

A Government-Mandated Procedural Change

Applicants can only apply for a marketing license in one of the member states using the Nationalized method.

1. A request for a national marketing authorization must be submitted to the relevant authority in the Member State.

Even though a novel active chemical is not mandated to go through the Centralized procedure, it can nonetheless get marketing approval through this route. There will be a 210-day window for this process.

With a decentralized approach, businesses can submit applications for approval in many EU countries at once for products that have not previously been permitted in any EU country and generally do not come within the essential drugs list used by the centralized system. Using this process, businesses can seek EU approval for items that have not previously been approved anywhere in the European Union.

The judgement reached by the RMS and CMS in this decentralized process should be used to provide a marketing permission. The RMS's evaluation report and any further insights provided by the CMS should form the basis of this choice.

This word describes products that have not received any type of approval from any EU member state.

Time: 210 days

Form 44 and the information needed by Schedule Y of the Drugs and Cosmetics Act 1940 and Rules 1945 must be submitted to the DCGI for review whenever a company in India plans to manufacture or import a new drug. Before the corporation can implement its ideas, this must be completed. It's feasible that he'll allow the entry of new drugs based on the findings of foreign clinical trials. This will help the Indian government show that the medicine is beneficial to the health of the Indian people and is safe to use. Clinical trials are required for all drug compounds in India according to Section 2.4 (a) of Schedule Y of the Drugs and Cosmetics Act 1940 and Rules 1945, as stated in Rule 122A.

Applicants for drug compounds found outside of India must present data easily available from such nations in accordance with Section 2.4 (b) of Schedule Y of the Drugs and Cosmetics Act 1940 and Rules 1945. The licensing body might make the applicant start again with all new research or let him go on from the Phase III trials.

Section 2.8 of Schedule Y of the Drugs and Cosmetics Act 1940 and Rules 1945 states that the licensing authority can require Phase III trials if the applicant cannot show that the data generated in the Indian population is equivalent to the data generated outside of India through pharmacokinetic studies (also known as bioequivalence studies).

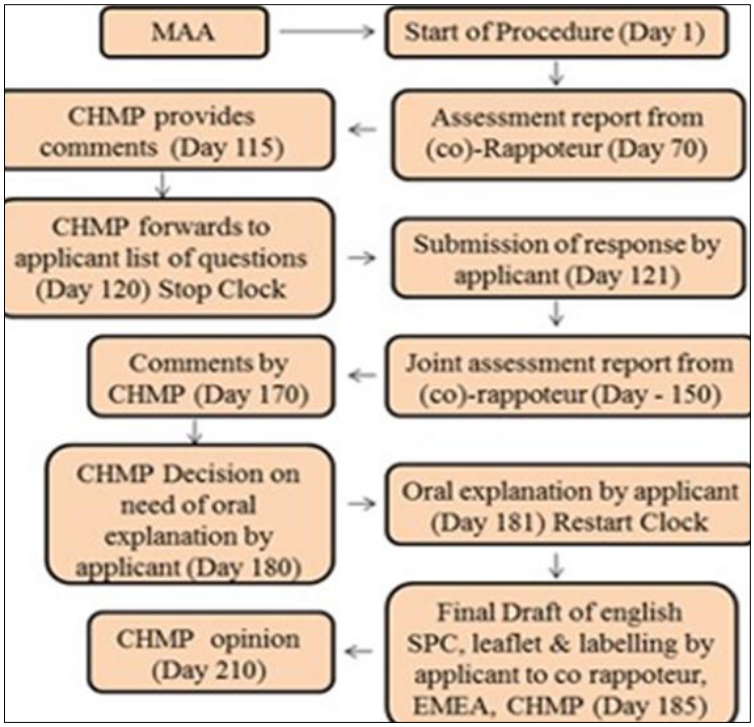

Fig 2: Centralized Procedure Expressed Graphically What It Takes to Get a New Drug Approved in India (7–10):

In a nutshell, the specific requirements of clinical trials may differ from one instance to the next, depending on the degree of satisfaction the licensing body has concerning the safety and efficacy of the product.

Obtaining approval for a novel drug in India is a lengthy process that requires applicants to me*et all* applicable requirements in addition to filing an NDA to the FDA. Due to the nature of the work at hand, it is required to research and document the steps involved in getting a new drug approved in India, with special attention paid to the role that clinical trials play in this process, as defined by the Drugs Control division of the Government of India.

New drug applications (NDAs) are submitted to the Food and Drug Administration (FDA) to gain marketing clearance for novel pharmaceuticals. Sponsors must first submit data from preclinical and clinical studies so that NDA may analyze the drug information and describe the production methods before receiving this authorization.

The NDA undergoes a technical review once it has been received by the agency. The purpose of this assessment is to ensure that all required information has been provided to support the "filing" of the application for official FDA review. This is done by evaluating how well the provided information "filing" requirements match the data and information provided. Once the FDA has finished reviewing an NDA, they may take one of three possible options and notify the sponsor:

The Indian medication approval process

Findings and Discussion

Table 1: Differences between the US, EU, and India that are worth noting

Requirements	US	EU	India
Agency	There Is but One Organization USFDA	Band of Ad Men	One Registration Process, One Agency DCGI
Registration Process	There is Only One Registration Process	Both the European Medicines Agency and the UK's Central Medicines Regulatory Agency are involved in health care.	Need TSE/BSE Study Information
TSE/BSE Study data	No need for TSE/BSE Study records		Putting a Braille symbol on a label is optional.
Braille code	Putting a Braille symbol on a label is optional.	Multiple-Registration Procedures	After the fact alterations:
Post-approval changes	Alterations made to the authorized medicine after its release:	Centralization a la European Union	Major improvements in quality

Table 2: Needed for Administrative Purposes

Requirements	ANDA/NDA in the	Non-Necessity of an	Not Necessary for
Disqualification of	United States	EU	INDIA's
Applications categorization	Required	MAA	MAA
Quantity Produced		12 months	12-18 month
Schedule for Acceptance	3.0	1	1 Between
Fees	NDA Application for amounts less than $2 million ANDA Application for $51,520	The national cost is currently set at £103,059 (including hybrid applications). Procedure that is decentralized and the UK is the CMS: £99,507	50,000 INR
Presentation	eCTD & Paper	eCTD	Paper

Table 3: Conditions for Finished-Item Control

Requirements	90-100%	95-100%	India
Justification	US	EU ICH	ICH Q6A 90 - 110%
Assay	ICH Q6A	Q6A	Required
Assay Disintegration	Absent Necessity	Required	Required
Color Identification	Absent Necessity	Required	Required
Quantity of Water	Absent Necessity	Not Required	INDIA

Table 4: Specifications for Manufacturing and Quality Control

Requirements	US	EU	India
Iterations counted	1	3	1
Packaging	A minimum of 1,00,000 Units	Not Required	Not addressed
Batch Size for	Do not need to be included at the time of submission	Either	Needed Small
Process Validation	1,000 minimum units or one pilot run	2 pilot-scale production runs and 1 lab batch, or 1,000,000 units, must be produced.	Scale Production Run

Table 5: Situations Calling for Stability

Requirements	US	EU	India
Quantity of Individuals	Three Small-Scale Runs or Two Pilot Runs and One Full-Scale Run	2 Pilot Scale (If API Stable) 3 Primary Batches (If API unstable)	2 Test on a Small Scale/Go Live if API Is Reliable 3 Primary Batches (In the Case of Unreliable API)
Stability throughout the long period, accelerated stability,	25 °C/60% RH in the long term 40 °C/75° RH (0, 3, 6 months) = rapid; 30 °C/65° RH = intermediate	25 °C/60% RH in the long term Acute: 40 °C/75% RH (3, 6 Months) Conditional on: 30 °C/65%RH	A constant 30 degrees Celsius and 70 percent relative humidity Accelerated:40 °C/75%RH (3,6 Months)
Time limit for submissions	6 Months Accelerate & 6 Months long term	Six months of fast track and six months of regular pay.	Six months of fast track and six months of regular pay.
Orientation of the Container	Inverted & Upright	Avoid talking about	right and upside down
QP	21 CFR part 210 & 211	EU Medicinal Products Directive, Volume 4	ICH Q1F
Accreditation Clause	Not Required	Required	Required

Table 6: Prerequisites for Bioequivalence

Requirements	US	EU	India
CRO (Audits)	Audited by FDA	Audited by MHRA	CDSCO
Reserve Sample	Analyze with 5 times the minimum sample size	Certainly not necessary	-
Fasted / Fed	Must be suggested by OGD.	Certainly not necessary	CDSCO
Retention of samples	Against US RLD in any nation, the application period is 5 years from the date of filing.	Certainly not necessary	suggests waiting three years from the application's submission date.
BE study for generic drugs	Be sure to check out the FDA's 'BE guidelines' for some pointers.	When compared to the European Union's (EU) ERP in each given nation	Against US/EU/Australia RLD everywhere except Thailand, where BE must be conducted domestically in comparison to a domestic standard.

Conclusion

Biosimilars show promise in lowering the price of therapy for a variety of cancers and other diseases, making them more widely available to patients. There has been a massive increase in the manufacture and usage of "biosimilars or similar biologics" since the first instance of their use. Similar biologics for the treatment of a wide range of malignancies and nonmalignant illnesses get annual approval from regulatory bodies. India has made a name for itself as a global leader in the production of similar biologics. Due of its large and growing population, it is also a promising market for comparable biologics. India has a lot of potential, and many people have high hopes for the country, but it faces formidable challenges if it is to maintain its current level of leadership. For the Indian biopharmaceutical sector to reach its full potential and continue to be a global leader, it must upgrade its technology and improve the skills of its workers. They will need government and regulatory agency backing to do this.

References

1. Rick NG. Drugs from discovery to approval. 2nd ed. John Wiley & Sons, Inc.; c2008. p. 201-202. 2.
2. IRA RB, Robert PM. The Pharmaceutical Regulatory Process. 2nd ed. Informa healthcare; 2008;45:3.
3. Rick NG. Drugs from discovery to approval. 2nd ed. John Wiley & Sons, Inc. 2008;4:203-210.
4. IRA RB, Robert PM. The Pharmaceutical Regulatory Process. 2nd ed. Informa healthcare; 2008;5:46-48.
5. Rick NG. Drugs from discovery to approval. 2nd ed. John Wiley & Sons, Inc. 2008;6:212-220.
6. IRA RB, Robert PM. The Pharmaceutical Regulatory Process. 2nd ed. Informa healthcare. 2008;7:49-51.
7. Clinical Trial & Global Clinical Trial [Internet]. [cited 2014 January]. Available from: http://cdsco.nic.in/clinical_trial.htm. 8.
8. The New Drug Approval Process [Internet]. [cited 2014 January]. Available from: http://www.fda.gov/cder/handbook. 9.

9. CDER Guidance: IND application process (interactive session) [Internet]. [cited 2014 January]. Available from: www.fda.gov/cder/regulatory/applications/ind_page_1.htm. 10.
10. Shaikh T. Role of chemistry in drug discovery and drug design. Int. J Adv. Chem. Res. 2021;3(1):16-18. DOI: 10.33545/26646781.2021.v3.i1a.30
11. Thorpe R, Wadhwa M. Terminology for biosimilars-a confusing minefield. GaBI J. 2012;1:132-134.
12. Rotenstein LS, Ran N, Shivers JP, *et al*. Opportunities and challenges for biosimilars: what's on the horizon in the global insulin market? Clin Diabetes. 2012;30:138-150.
13. Owens DR, Landgraf W, Schmidt A, *et al*. The emergence of biosimilar insulin preparations: A cause for concern? Diabetes Technol Ther. 2012;14:989-996 [PMC free article]
14. Heinemann L. Biosimilar insulins. Expert Opin Biol Ther. 2012;12:1009-1016.
15. Gough S. Biosimilar insulins: opportunities and challenges. Pract Diabetes. 2013;30:146-148.
16. World Health Organization: Guidelines on Evaluation of Similar Biotherapeutic Products (SBPs). Expert Committee on Biological Standardization, Geneva, 19-23 October 2009. www.who.int/biologicals/areas/biological_therapeutics/BIOTHERAPEUTICS_FOR_WEB_22APRIL2010.pdf (accessed January27, 2014)
17. International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use: ICH Guidelines. www.ich.org/products/guidelines.html (accessed August13, 2014)
18. Parker GE, Witwer S, Miller Bowker G: Regulatory Approval of Biosimilars: A Global Perspective. RAPS Regulatory Focus January 2014. www.raps.org/regulatoryDetail.aspx?id=9837 (accessed August13, 2014)
19. Scheinberg MA, Kay J. The advent of biosimilar therapies in rheumatology- O brave new world." Nat Rev Rheumatol. 2012;8:430-436.
20. European Medicines Agency: EMA Guideline on Similar Biological Medicinal Products. 2005. www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003517.pdf (accessed August13, 2014)
21. European Medicines Agency: EMA Guideline on Similar Biological Medicinal Products. Draft. 2013. www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2013/05/WC500142978.pdf (accessed August13, 2014)
22. European Medicines Agency: EMA Guideline on Non-Clinical and Clinical Development of Similar Biological Medicinal Products Containing Recombinant Human Insulin and Insulin Analogues. Draft. 2014. www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2014/04/WC500165988.pdf (accessed August13, 2014)
23. U.S. Food and Drug Administration: Scientific Considerations in Demonstrating Bio similarity to a Reference Product; c2012.
24. Guidance for industry on preparation of common technical document for import/ manufacture and marketing approval of new drugs for human use. (New Drug Application–NDA) [Internet]. [cited 2014 January]. Available from: http://cdsco.nic.in/CTD_Guidance%20- Final.pdf.