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COMPARISON BETWEEN USFDA AND EU REGULATORY MARKETS IN PHARMACEUTICALS

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Abstract:

Regulatory Affairs in the pharmaceutical business is coping with all aspects of state affairs and to fulfil the wants of the company administrative body of the involved nations and deals with getting the approval from the license, development of a pharmaceutical product to production, drug approval method and registration of pharmaceutical merchandise available and distribution in numerous regulated markets and for post promoting studies. The pharmaceutical firms should obey the legislations that need medicine to be developed, tested, trailed, and made in accordance with the rules in order that they're safe and their well-being is protected. The FDA regulates medical pharmaceuticals and devices with competing aims of ensuring safety and efficacy while also allowing novel therapies to advance quickly through the investigation and regulatory processes. The United States and the European Union take different approaches to these issues. The European Commission synchronised the legislation of 28 distinct countries as they merged to form the European Union, but the United States has always depended on a strictly centralised method through one agency, the Food and Drug Administration (FDA). The FDA began as a consumer protection body, but the European Commission's laws evolved from a desire to reconcile inter-state commercial interests while maintaining national "autonomy."

Key words: *Regulatory Affairs, drug approval, pharmaceutical Industry, USFDA, EU regulatory markets.*

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INTRODUCTION:

Before a brand-new drug or biological will attend the market, a drug submission should be assembled and filed with all relevant regulative agencies to appear for a review and, ultimately, regulative approval. [1] every jurisdiction has its own procedures to review drug submissions filed to their regulatory authority. [2] These procedures will disagree considerably with relation to how the drug submission is handled, the composition of the review team, review timelines so on. [4] America & Europe square measure the 2 main regulative agencies within the world.The United States may be a single country however EU may be a union of nations. Therefore, the Drug approval method in each the regulative agencies has been summarized for straightforward understanding. [5]

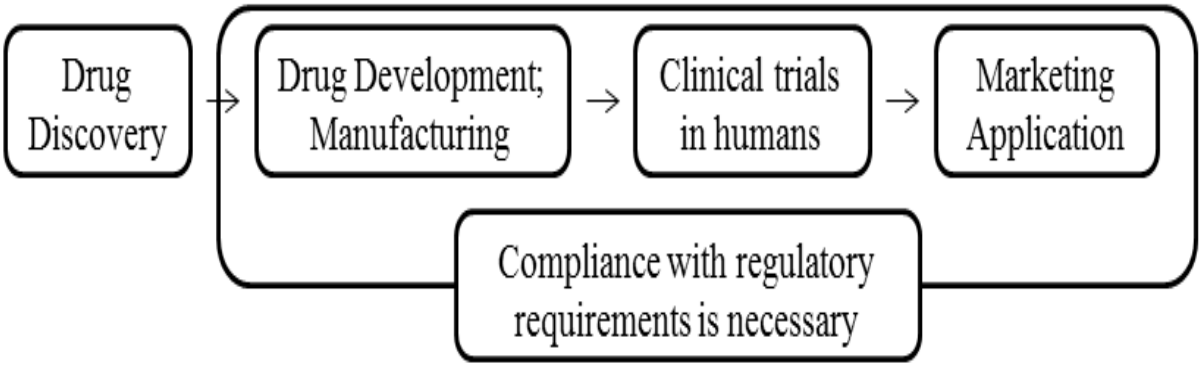

Figure 1: Flow chart of drug development

Drug Approval in United States:

The us has maybe the world's most rigorous standards for approving new medicine. Drug approval standards within the us square measure thought of to be the foremost hard within the world. [6-8] Following square measure some vital terms and definition utilized in the restrictive filings is delineate below.

- FILING: A document that an organization should send to an officer organization that regulates its activities.
- DOSSIER: A document that contains all the technical knowledge (administrative, quality, nonclinical and clinical) of a pharmaceutical product to be approved / registered marketed during a country.
- Drug computer file: A Drug Master File (DMF) may be a submission to the FDA that will be accustomed offer confidential elaborate info concerning facilities, processes, or articles utilized in the producing, processing, packaging, and storing of 1 or a lot of human medicine.
- Type I: producing web site, Facilities, operative Procedures, and Personnel (No longer accepted by FDA).
- Type II: Drug Substance, Drug Substance Intermediate, and Material utilized in their Preparation, or Drug Product.
- Type III: Packaging Material.
- Type IV: Excipient, Colorant, Flavour, Essence, or Material utilized in their Preparation.
- Type V: FDA accepted Reference info (FDA discourages its use).

Investigational New Drug Application (INDA):

It's an application filed to the FDA so as to begin clinical trials in humans if the drug was found to be safe from the reports of diagnosing trials. It provides resources to help drug sponsors with submitting applications for approval to start new drug experiments on human subjects.

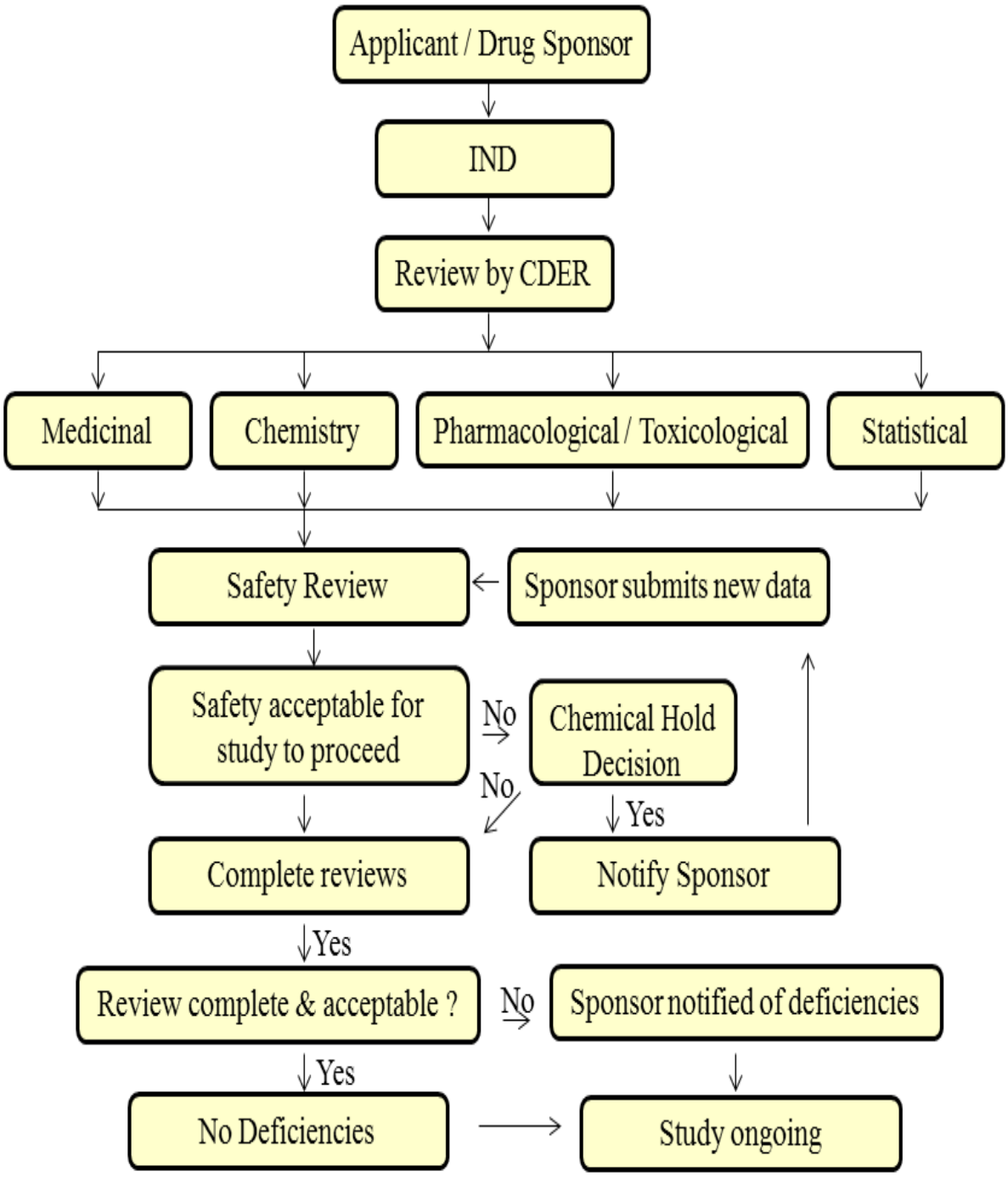

Figure 2: Investigational New Drug Application (INDA)

New Drug Application (NDA):

If clinical studies make sure that a replacement drug is comparatively safe and effective, and can not cause unreasonable risks to patients, the manufacturer files a replacement Drug Application (NDA), the particular request to manufacture and sell the drug within the US. Provides resources to assist drug sponsors with submitting applications for approval to promote a replacement drug. [10-11]

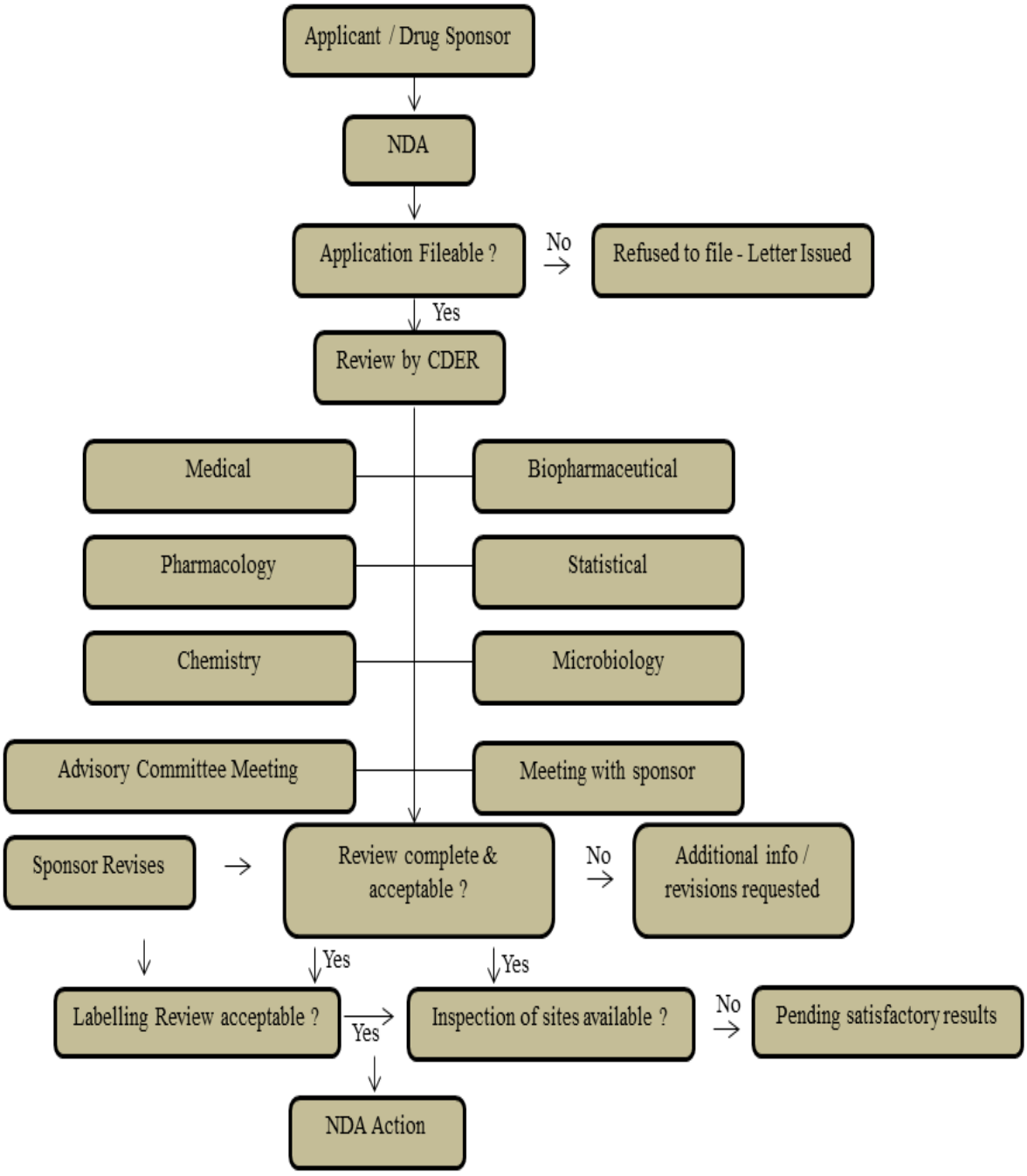

Figure 3: New Drug Application

Abbreviated New Drug Application (ANDA):
It's an application made for approval of Generic Drugs. The sponsor is not required to reproduce the clinical studies that were done for the original, brand name product. Application for the review and ultimate approval of generic drugs. [12]

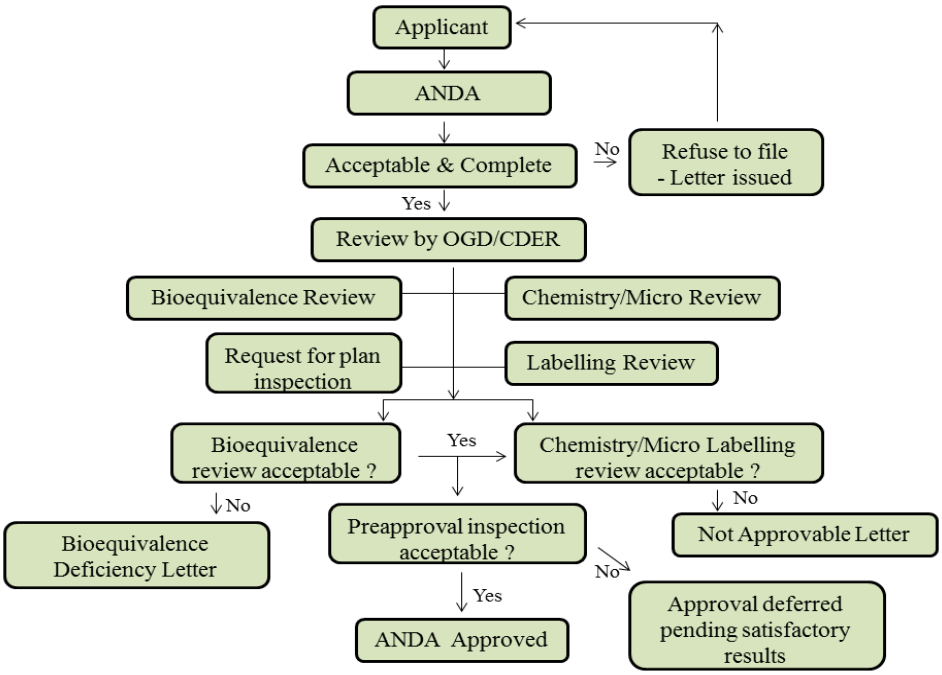

Figure 4: Generic Drug Approval (ANDA Approval)

Drug Approval in Europe:

- Mutual Recognition Procedure: medicine authorized in one EU Member State can apply for this authorization to be recognized in other EU countries.
- Nationalized Procedure: marketing authorization in one-member state only.
- Decentralized Procedure: simultaneous authorization of a medicine in more than one EU country if it has not yet been authorized in any EU country and it does not fall within the mandatory scope of the centralized procedure.
- Centralized procedure: The centralized procedure is one which allows applicants to obtain a marketing authorization that is valid throughout the EU. [13]
- Results in a single authorization valid in EU, Norway, Iceland and Liechtenstein.
- Application evaluated by an assigned Report.
- Timeline: EMA opinion issued within 210 days, and submitted to European Commission for final approval.

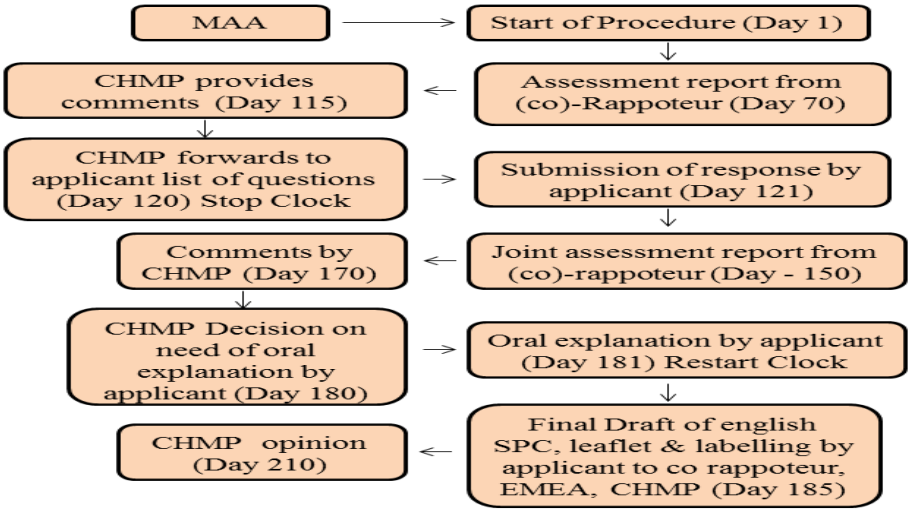

Figure 5: Centralized Procedure

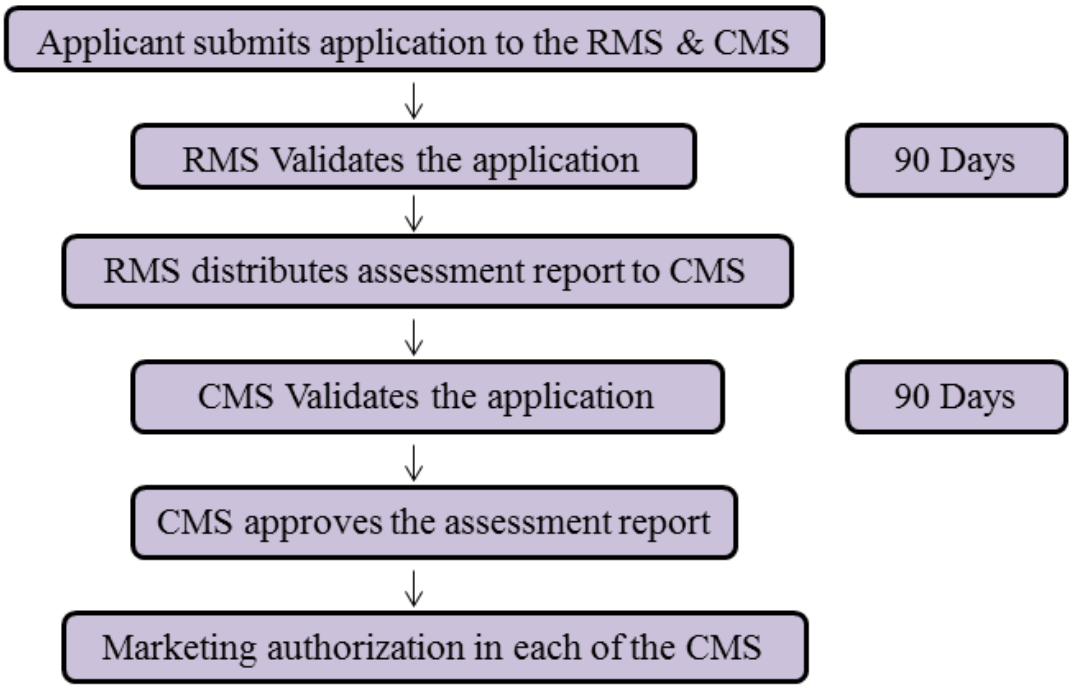

Figure 6: Mutual recognition procedure

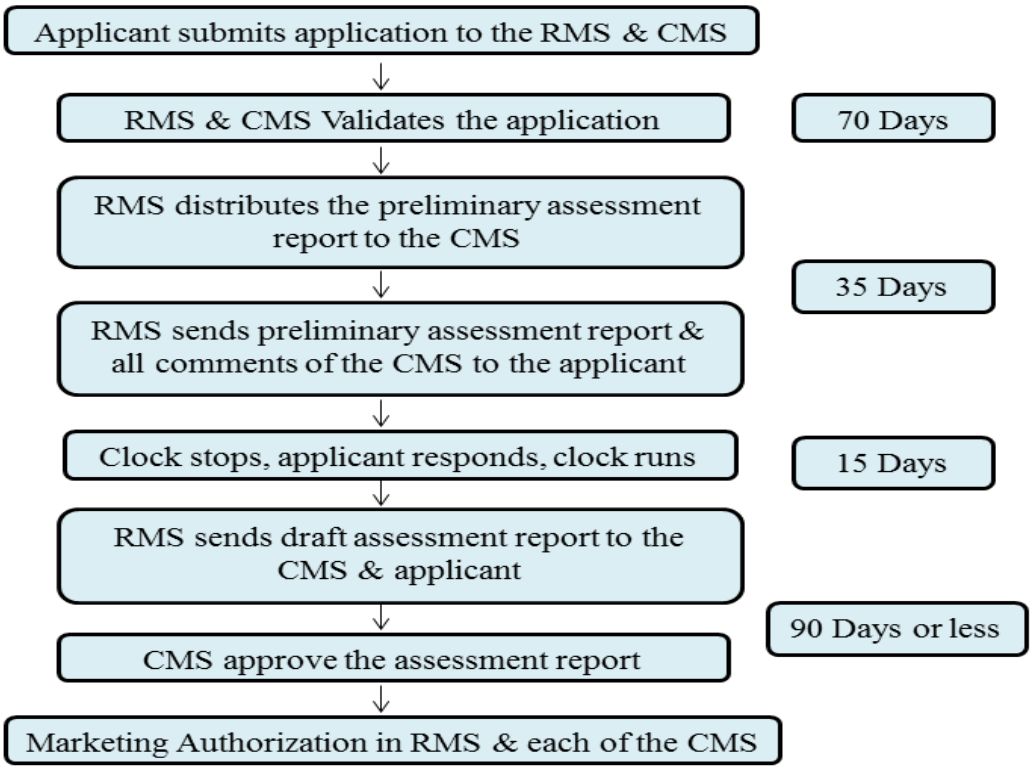

Figure 7: Decentralized Procedure

Principle Difference Between USFDA and EU:

Table 1: Difference between USFDA and EU

USFDA	EU
One agency.	Multiple agencies. EMEA CHMP National Health Agencies
One Registration Process.	Multiple Registration Process: Centralized (European Community) Decentralized (At least 2 member states). Mutual Recognition (At least 2 member states). National (1-member state)
TSE/BSE study data not required.	TSE/BSE study data required.
Braille Code is not required on Labelling.	Braille Code is required on Labelling.
The changes in the approved drug can be done by filing: PAS CBE - 30 /CBE Annual	The changes in the approved drug can be done by filing: Type IA Variation Type IB Variation Type II Variation

Administrative Requirements:

Table 2: Administrative Requirements

SR.NO.	REQUIREMENTS	USFDA	EU
1.	Application	ANDA/NDA	MAA
2.	Debarment Classification	Required	Not Required
3.	No. of copies	3	1
4.	Approval Time	18 Months	12 Months
5.	Fees	No fees	10 – 20 Lakhs
6.	Presentation	eCTD & Paper	eCTD

Finished Product Control Requirements:

Table 3: Finished Product Control Requirements

SR.NO.	REQUIREMENTS	USFDA	EU
1.	Justification	ICHQ6A	ICHQ6A
2.	Assay	90-100%	95-105%
3.	Disintegration	Not Required	Required
4.	Colour Identification	Not Required	Required
5.	Water Content	Required	Not required

Manufacturing and Control Requirements:

Table 4: Manufacturing and Control Requirements

SR.NO.	REQUIREMENTS	USFDA	EU
1.	No. of Batches	1	3
2.	Packaging	A minimum of 1,00,000 Units	Not Required
3.	Process Validation	Not Required at the time of submission	Required
4.	Batch Size	Minimum of 1,00,000 Units.	Minimum of 1,00,000 Units.

Stability Requirements:

Table 5: Stability Requirements

SR.NO.	REQUIREMENTS	USFDA	EU
1.	No. Batches	1	2
2.	Condition	25/60 – 40/75	25/60 – 40/75
3.	Date & Time of Submission	3 Months Accelerate & 3 Months Long Term	6 Months Accelerate & 6 Months Long Term
4.	Container Orientation	Inverted & Upright	Do not address
5.	Clause	21 CFR Part 210 & 211	VOL 4 EU Guidelines for Medicinal Products
6.	QP Certification	Not Required	Required

Bioequivalence Requirements:

Table 6: Bioequivalence Requirements

SR.NO.	REQUIREMENTS	USFDA	EU
1.	CRO	Audited by FDA	Audited by MHRA
2.	Reserved Samples	5 times the sample required for analysis	No such Requirement
3.	Fasted / Fed	Must be as per OGD Recommendation	No such Requirement
4.	Retention of Samples	5 years from date of filing the application	No such Requirement

CTD:

The Common Technical Document (CTD) may be a set of specification for application written account for the registration of Medicines and designed to be used across Europe and also the us. it had been developed by the ecu Medicines Agency (EMEA, Europe), the Food and Drug Administration (FDA, U.S.). The CTD is maintained by the International Conference on Harmonisation of Technical necessities for Registration of prescribed drugs for Human Use (ICH). The CTD was designed to produce a typical written account filing format between U.S and European countries for the registration of latest drug product. [14)]

The major pharmaceutical markets within the world us and world organization have completely different necessities for the registration of a pharmaceutical product. To coordinate the wants as per the restrictive agencies, an idea of common technical document and its electronic version was enforced by the ICH. [15] CTD is organized into 5 modules. Module one is region specific and Modules two, 3, four and five ar supposed to be common for all regions.

The CTD consists of five modules describing the subsequent details:

- Module1: body and prescribing data
- Module2: summary and outline of modules three to five
- Module3: Quality overall outline (pharmaceutical documentation)
- Module4: Non clinical document Safety (toxicology studies)
- Module5: Clinical document effectiveness (clinical studies).

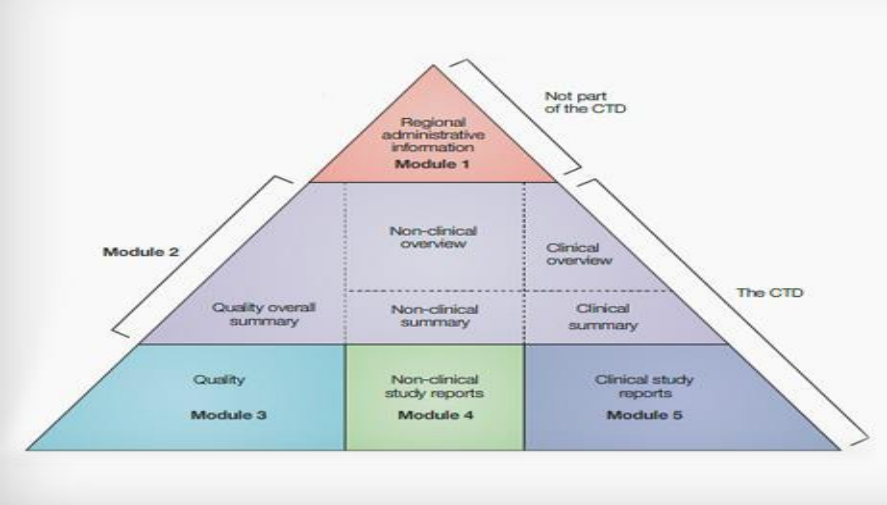

Figure 8: CTD

Significance of Common Technical Document:

- Avoid generating and assembling totally different registration written record
- Common format considerably can scale back time and resources
- Facilitates the coinciding submission in ICH 3 region
- Facilitate exchange of knowledge among regulative authorities
- Faster accessibility of recent drugs
- Enable the convenience and quick submission
- It is multidisciplinary in nature thus wide acceptable
- Throughout the CTD, the show of knowledge ought to be unambiguous and clear, to facilitate the review of the fundamental information and to assist a reviewer become quickly orienting to the applying contents.
- More predictable format
- More consistent review [16]

Limitations of CTD:

- CTD is barely a format; it's not one written record with one content.
- Legal needs dissent within the totally different regions
- ICH tips haven't nevertheless harmonic all told needs
- Pharmacopoeias aren't harmonic
- Applicant could have regional preferences

eCTD:

eCTD or electronic common technical document is Associate in Nursing interface designed for the pharmaceutical trade to transfer regulative data. This module-based regulative application format was developed by the International Conference on Harmonization (ICH money supply EWG). In 2008 the bureau (Food and Drug Administration) created eCTD format required for all electronic submissions by bureau in 2008. [17]

The role of eCTD is to assist pharmaceutical corporations enhance the submission procedure by bridging the gap between the time and market and minimizing expenses.

The eCTD could be a standardized arrangement of documents that permits for the consistent and comprehensive presentation of knowledge at intervals a submission. eCTD submissions embody five elements, termed modules, with every containing a particular kind of data.

- Module one (not technically a part of the CTD): region-specific body data
- Module 2: producing, nonclinical, and clinical overviews and summaries
- Module 3: elaborate producing data
- Module 4: nonclinical study reports
- Module 5: clinical study reports [18]

Blessings of eCTD:

- eCTD is constructed on acknowledged standards that haven't modified a lot of all told these years in integration ICH needs
- Regulative tools accustomed review submissions are upgraded and thence provide durable performance
- It follows a standard format for each America & Europe with comparatively easy changes (Module one and STF acceptance)

- The life cycle offers elaborate submission history along-with simple information transfer for product
- Consolidated formation offers transparency to submissions –
- Easy tools area unit used for -Publishing Submissions
- Methodology is kind of just like paper work
- Share the updates with multiple native affiliates concerned within the submission processes
- Viewer isn't needed throughout the submission method
- Cheap implementation

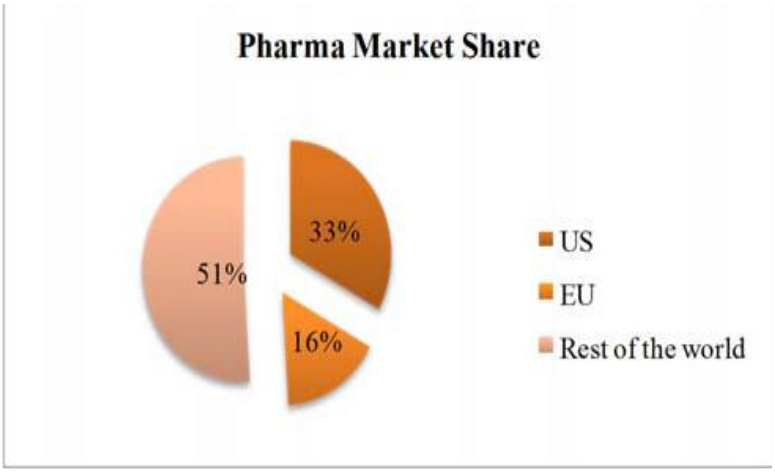

Figure 9: Pharma Market Share

CONCLUSION AND SUMMARY:

- Drug approvals within the us and Europe square measure the foremost exigent within the world.
- the first purpose of the foundations governing healthful product in USA and Europe is to safeguard public health.
- It's the role of public restrictive authorities to make sure that pharmaceutical corporations fits rules.
- There square measure legislations that need medication to be developed, tested, trailed, and made in accordance to the rules in order that they're safe and patient's well - being is protected.

REFERENCES:

1. Raji K, Aanandhi VM. Regulatory Filing In Us and Eu: A Comparative View. Res J Pharm and Tech. 2017;10(1):286-92.
2. Kashyap UN, Gupta V, Raghunandan HV. Comparison of drug approval process in United States & Europe. J Pharm Sci and Res. 2013 Jun 1;5(6):131.
3. Raji K, Aanandhi VM. Regulatory Filing In Us and Eu: A Comparative View. Res J Pharm and Tech. 2017;10(1):286-92.
4. Health Canada. (2011, March 29). Guidance for industry: Management of drug submissions.RetrievedJuly 18, 2012, from http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applicdemande/ guide-ld./mgmt.-gest/mands_gespd-eng.php#a5.2.
5. Rick NG. Drugs from discovery to approval. 2nd ed. John Wiley & Sons, Inc., (Hoboken, New Jersey). p. 201.
6. IRA R Berry, Robert P Martin, editors. The Pharmaceutical Regulatory Process. 2nd ed. Informa healthcare. p.48.
7. Rick NG. Drugs from discovery to approval. 2nd ed. John Wiley and Sons, Inc., (Hoboken, New Jersey). p. 212-14.
8. Rick NG. Drugs from discovery to approval. 2nd ed. John Wiley and Sons, Inc., (Hoboken, New Jersey). p. 215-17.
9. Rick NG. Drugs from discovery to approval. 2nd ed. John Wiley & Sons, Inc., (Hoboken, New Jersey). p. 203-4.
10. Rick NG. Drugs from discovery to approval. 2nd ed. John Wiley & Sons, Inc., (Hoboken, New Jersey). p. 205-7.
11. Rick NG. Drugs from discovery to approval. 2nd ed. John Wiley & Sons, Inc., (Hoboken, New Jersey). p. 208-10.
12. IRA R Berry, Robert P Martin, editors. The Pharmaceutical Regulatory Process. 2nd ed. Informa healthcare. p. 46.

13. Rick NG. Drugs from discovery to approval. 2nd ed. John Wiley & Sons, Inc., (Hoboken, New Jersey). p. 212-14.
14. Singh Satbir, Kumar Pankaj, and Rana Arpana, Global Regulatory Challenges of Common Technical Document, World Journal of Pharmacy and Pharmaceutical Sciences, Vol.6, Issue 12, 2017.
15. Sharma D, Sharma V, Shrivastava B and Songara R, "Comparative study of dossier files submission process for drug product in United states and Europe", Pharmacology online, 2011; 2: 337-362.
16. Bhalodiya HA, Boda JM, Shah JS, Patel PB and Vaghela JP, "The Common Technical Document: Taking Indian NDA process towards globalization", International Journal of pharmaceutical Science Review and Research, 2011; 30: 181-187.
17. Sharma D, Sharma V, Shrivastava B and Songara R, "Comparative study of dossier files submission process for drug product in United states and Europe", Pharmacology online, 2011; 2: 337-362.
18. Nisar Ahammad, Nagarjuna Reddy, M.V. Nagabhushanam, Brahmaiah Ramakrishna, Challenges faced during eCTD and CTD filing Procedures for USFDA and Canada, Journal of Drug Delivery and Therapeutics, 2019.
19. Joseph Lincy, George Mathew, Malaviya Kalpesh K, Chalco Bincy, Badjatya Jitendra K, Comparative Study for Generic drug approval process and their registration as per CTD in Europe, USA, and Brazil, International Journal of Drug Regulatory Affairs, 2016.
20. Mulaje SS, Birajdar S M, Patil B R, Bhusnure OG, Procedure for Drug approval in Different countries: A review, Journal of Drug Delivery and Therapeutics, 2011.
21. Indu Gurram, M.V.S. Kavitha, Nagarjuna Reddy, M V Nagabhushanam, Drug Master Filing in US, Europe, Canada and Australia, Review Article, Journal of Pharmaceutical Research, Vol.16, Issue 2, Apr-Jun, 2017.
22. Bhardwaj S, Budhwar V and Gupta VK, "Comparative study: Requirements for the submission of generic drug application across US & EU in CTD/eCTD format", Asian Journal of Pharmaceutical Science and Research, 2011; 1: 1-13.
23. Songara R, Shrivastava B, Sharma D and Sharma V, "Comparative study of dossier files submission process for drug product in United states and Europe", International Journal of Pharmaceutical Research and Development, 2011; 3: 60-78.
24. Holbein ME, "Understanding FDA Regulatory Requirements for Investigational New Drug Applications for Sponsor-Investigators", Journal of investigative medicine, 2009; 57: 689-695
25. Chavan PN, Vijayan S, Joshi MM, Godse N, Marialouis J, Kasibhatta R. Marketing authorisation procedures in Europe: A Regulatory perspective. International Journal of Pharmacy & Pharmaceutical Science Research. 2011; 1(1):13-19.
26. Ellender D, Marangoni E. EFPIA workshop: The 2001 review of European Union Pharmaceutical
27. Legislation. International Journal of Pharmaceutical Medicines. 2001; 15(3):140-9.
28. Nordfield K, Strasberger V. Creating eCTD applications. Journal of generic Medicines. 2006; 3(2):140-6.
29. Teresa M, Miguel S, Vagas E. Drug evaluation and approval process in the European Union. 2006;55(1):12-14.
30. U.S. Food and Drug Administration. (2005, April). Guidance for Review Staff and Industry. Good Review Management Principles and Practices for PDUFA Products. Retrieved July18,2012, fromhttp://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidance/ucm079748.pdf.
31. Grignolo, A. (2008). Meeting with the FDA. In Pisano, D.J. and Mantus, D.S. (Eds.) FDA regulatory affairs: A guide for prescription drugs, medical devices, and biologics (2nd ed., pp.109-23). New York: Informa Healthcare.
32. European Medicines Agency. (2012, April). European Medicines Agency pre-authorisation procedural advice for users of the centralised procedure. Retrieved September 26, 2012,http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/10/WC500004069.pdf.
33. Sahoo U and Kumar N, The Regulatory Affairs Profession in India, *The Regulatory Affairs Journal –Pharma*, 2007, **19**(1), 25-28.
34. Guidelines for Drug Master Files [Internet]. CDER, FDA; 2005 Mar [cited 2015 Nov 15]. Availablefrom:http://www.FDA.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm122886.htm (Accessed on 15th march 2017).
35. Dylst P, Vulto A, Simoens S. Overcoming challenges in market access of generic medicines in the European Union. Journal of Generic Medicines. 2012;9(1):21-8.
36. "Generic Drugs", U.S. Food and Drug Administration. Available from: http://en.wikipedia.org/wiki/U.S._Food_and_Drug_Administration [accessed23.11.2017.

37. Rahul R, *et al*. Comparative Study of Generic Drug Approval in EU, USA and China. Int J Pharm Sci Rev Res. 2017;42(2):67-73.
38. Ramana MV, *et al*. Generic Drug Registration Procedure in US and European Markets. Am J Pharm Health Res. 2014;2(11):12-21.
39. Siddharth NS, Pethani T and Sheth NR. A review on comparison of regulatory requirements to approved drug device combination products in Europe and USA. World J Pharm Pharm Sci 2014; 3: 455–475.
40. Vihar K. Regulatory strategy for registration of combination products to us-FDA. International Journal of Drug Regulatory Affairs 2014; 2: 27–42.
41. Hirako M, McAuslane N, Salek S, Anderson C, Walker S. A comparison of the drug review process at five international regulatory agencies. Drug Inf J 2007;41: 291-308.
42. PanteliD, Arickx F, Cleemput I, et al. Pharmaceutical Regulation in 15 European Countries: Review. Geneva, Switzerland: Word Health Organization; 2016.