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Generic Drug Registration Procedure in US and European Markets

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ABSTRACT

This topic aims at reviewing the drug filing and different aspects of obtaining United States Food & Drug Administration (USFDA) and European Medicines Agency (EMA) approval for a drug in order to get a Marketing Authorization in US &Europe and their effective role in improving the standards laid down by them. The goal of the approval process is to provide enough information about the drug safety and efficacy in human beings. ANDA is a regulatory submission for authorization of generic version of New Drugs after expiry of its patent period in US. Marketing authorization application is filed with the relevant authority in the Europe (typically, the UK's MHRA or the EMA's Committee for Medicinal Products for Human use (CHMP)) to market a drug or medicine. In Europe there are four types of marketing authorization procedures like national procedure (NP), centralized procedure (CP), decentralized procedure (DCP) and mutual recognition procedure (MRP) for getting generic drug approval process. The Common Technical Document (CTD) is a set of specification for application dossier, for the registration of Medicines and designed to be used across Europe, and the United States. Quality, Safety and Efficacy information is assembled in a common format through CTD.

Keywords: Generic drugs, drug approval process, ANDA, MAA, CTD format.

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INTRODUCTION

A generic medicine is a medicinal product which has the same qualitative and quantitative composition in active substances, has the same strength, pharmaceutical form and administration route as the originator medicine, and whose bio-equivalence with the originator medicine has been demonstrated by appropriate bio-availability studies A generic medicine has the same quality, safety and efficacy as the originator medicine and, therefore, generic and originator medicines are interchangeable [1, 2].

Generic Drug approval in United States

Abbreviated New Drug Applications (ANDA)

- An Abbreviated New Drug Application (ANDA) contains data submitted to FDA's Center for Drug Evaluation and Research, Office of Generic Drugs, for review and ultimate approval of a generic drug product.
- Once ANDA is approved, an applicant may manufacture and market the generic drug product to provide a safe, effective, low cost alternative to the public [3].

Types of Certifications

The generic makes one of four certifications for each patent:

Paragraph (I): that no patent information on that brand name drug has been submitted to the FDA.

Paragraph (II): that the listed patent has expired.

Paragraph (III): that the listed patent will expire on a certain date, before which time the generic will not enter the market.

Paragraph (IV): that the patent is invalid or will not be infringed by the manufacture, use, or sale of the new drug for which the ANDA was submitted [4]. When the generic makes a paragraph I or II certification, the FDA may approve its ANDA immediately. The FDA may approve a paragraph III certification anytime after the patent's expiration date. The implications of a paragraph IV certification are not nearly as simple. A generic makes a paragraph IV certification when it does not want to wait for the expiration of the pioneer's patent rights before it begins to market its own generic version of the drug. Instead, it alleges that it is justified in early market entry because its drug does not infringe the pioneer's patent or because the patent is invalid.

Filing of Anda

- In order to file ANDA all required items should be in proper order (organization). Detail information is available under Regulation 21 CFR 314.50, 21 CFR 314.94 and 21 CFR

314.440 [5, 6].

- Office of Generic Drug (OGD) strongly encourages submission of the bioequivalence, chemistry and labeling portions of an application in electronic format (Figure. 1).

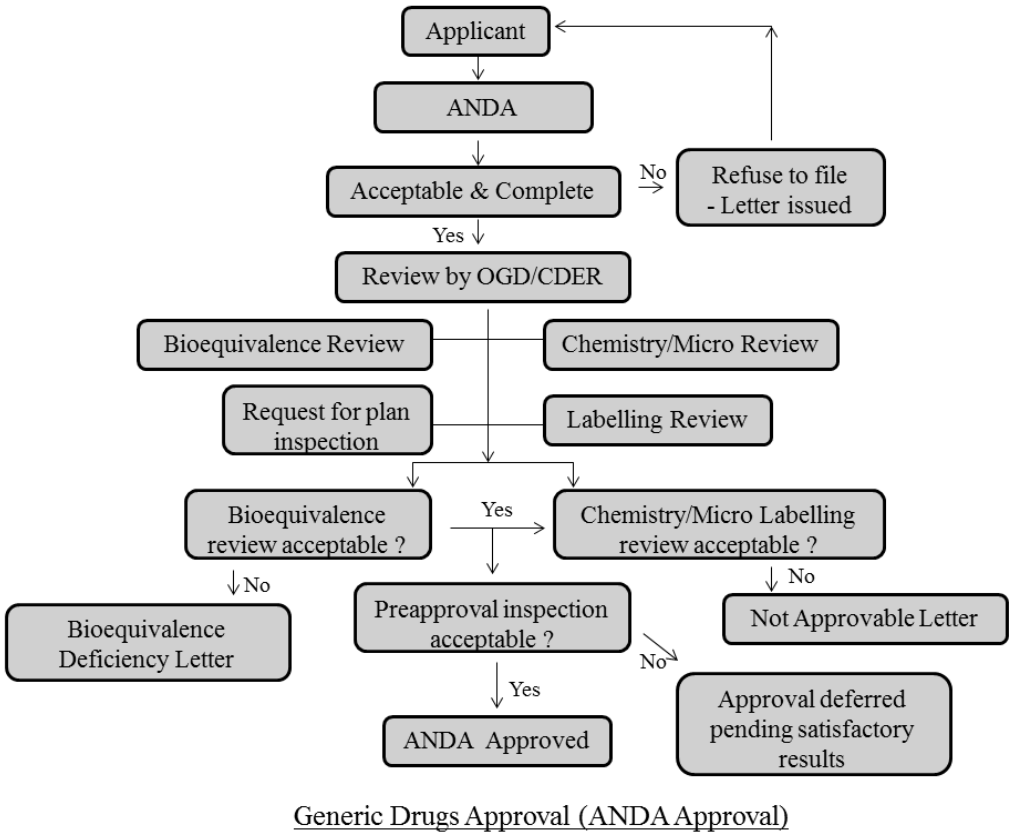

Figure. 1: Abbreviated new drug application (for generic drugs)

Generic drug approval in Europe

For marketing authorization of the generic medicinal product in Europe, the applicant should submit abridged application to the relevant authority. The marketing authorization is done by the following types of procedures [7]. They are

1. Centralized procedure
2. National procedure
3. Decentralized procedure
4. Mutual recognition procedure

Centralized procedure

The centralized procedure was enforced in the EU in 1995.

A marketing authorization granted under the centralized procedure is valid for the entire Community market, which means the medicinal product, may be put on the market in all the Member States. Iceland, Liechtenstein and Norway have, through the European Economic Area

agreement, adopted the complete Community acquis on medicinal products, and are Consequently parties to the centralized procedure (Figure. 2). Medicinal products derived from biotechnology like Recombinant DNA technology, Hybridoma and monoclonal antibody methods and biotechnology products which would be considered obligatory for the centralized procedure are like products intended for gene therapy; vaccines from strains and cell therapy products. New Active Substances "mandatory scope" medicines are intended use for the treatment of acquired immune deficiency syndrome, cancer, neurodegenerative disorder, and diabetes. Applications for medicinal products designated as orphan medicinal products must use the centralized procedure. The Timeline for this procedure is 210 days [8].

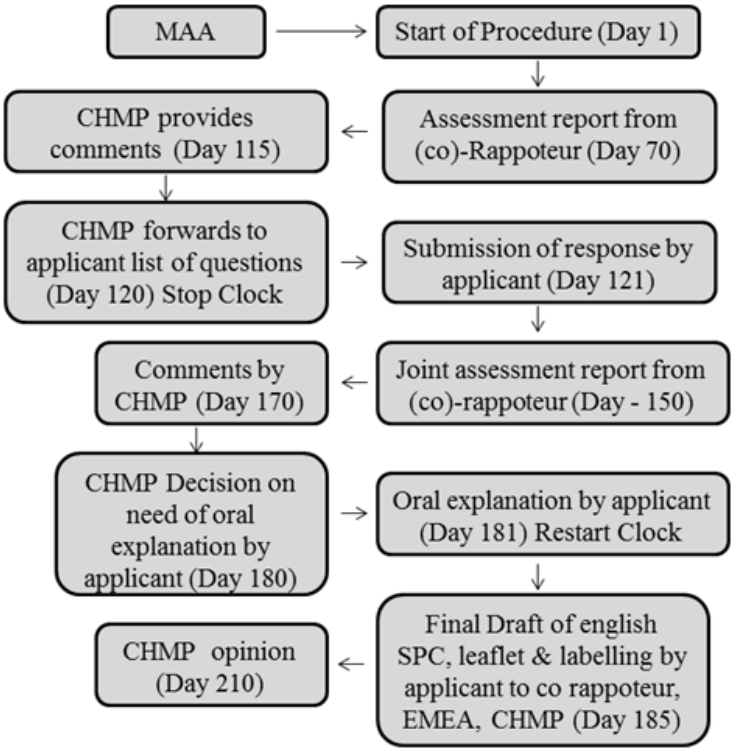

Figure. 2: Centralized procedure

National procedure

Each EU Member State has its own procedures for the authorisation of medicines that fall outside the scope of the centralized procedure. Applicants must submit an application to the competent authority of the Member State. The Applicants will receive assessment reports for major, standard and complex national initial applications. The assessment report will be sent to the applicant with the request for further information at the initial assessment stage. Following the applicant's submission of responses, a new assessment report (containing the assessment of the responses only) will be sent to the applicant. These reports will help applicants better

understand the context and basis of the comments raised by assessors.

The Timeline for this procedure is 210 Days [9].

Decentralized procedure

The new Decentralized procedure was enforced in the EU in 2005. The decentralized procedure is to be used in order to obtain marketing authorizations in several Member States where the medicinal product in question has not yet received a marketing authorisation in any Member State at the time of application.The procedure to be followed will depend upon whether it is a Member State or the Marketing authorisation holder which initiates the decentralized procedure (Figure. 3). The time line for Decentralized procedure is 210 days [10].

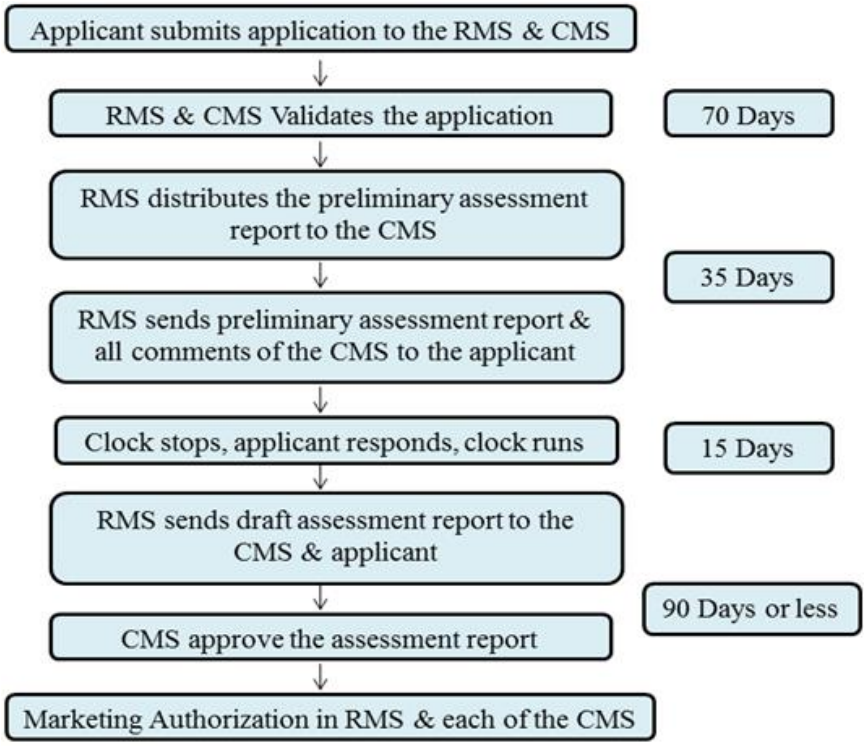

Figure. 3: Decentralized procedure

The mutual recognition procedure

The mutual recognition procedure was enforced in the EU in 1995. The mutual recognition procedure is to be used in order to obtain marketing authorizations in several Member States where the medicinal product in question has received a marketing authorisation in any Member State at the time of application. The procedure to be followed will depend upon whether it is a Member State who triggers or the marketing authorisation holder who initiates the mutual recognition. Thus with the exception of those medicinal products which are subject to the centralized procedure a marketing Authorisation or the assessment in one Member State (the so-

called reference Member State (RMS)) ought in principle to be recognized by the competent authorities of the other Member States (the so-called concerned Member States (RMS)), unless there are grounds for Supposing that the authorisation of the medicinal product concerned may present a Potential serious risk to public health. The time line for mutual recognition procedure (Figure. 4) is 90days [11].

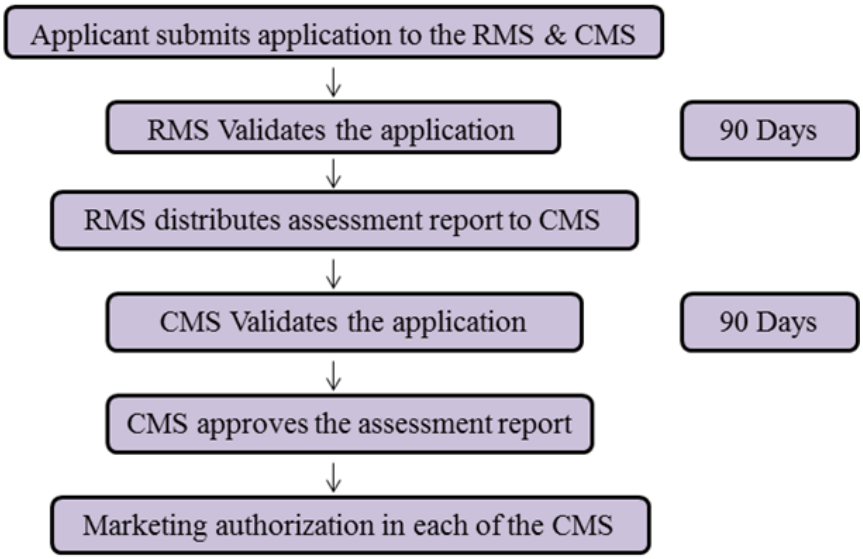

Figure. 4: Mutual Recognition Procedure

Dossier Submission of CTD Format in US and Europectd

The Common Technical Document (CTD) is a set of specification for application dossier, for the registration of Medicines and designed to be used across Europe, Japan and the United States.Quality, Safety and Efficacy information is assembled in a common format through CTD (Fig.5).The CTD is maintained by the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) [12].

Modules in CTD

The Common Technical Document is divided into five modules:

Module 1 – Administrative information and prescribing information (Table 1)

Module 2 – Common Technical Document summaries (Table 2)

Module 3 – Quality (Table 3)

Module 4 – Nonclinical Study Reports (toxicology studies)

Module 5 – Clinical Study Reports (clinical studies) (Table 4)

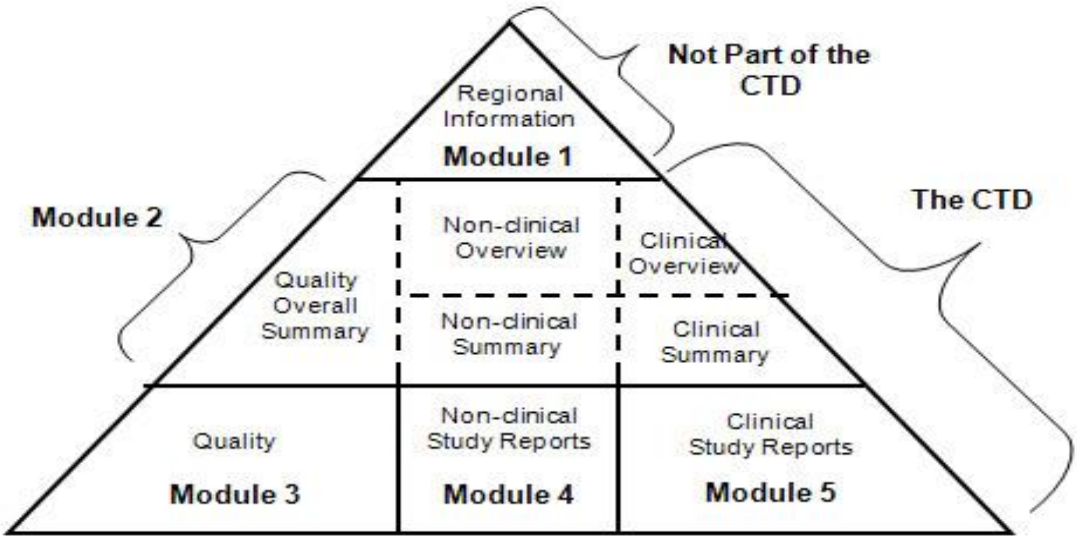

Figure. 5: CTD triangle

Differences Between US and Europe CTD Format

Table 1: Module 1 - Administrative Information and Prescribing Information

IN US	IN Europe
Signed and Completed Application Form (356h) **Form FDA 3674**	Marketing authorization Application Form
Cover Letter	**Cover Letter**
Debarment Certification-GDEA (Generic Drug Enforcement Act)/Other: (no qualifying statement) 1. Debarment Certification (original signature) 2. List of Convictions statement (original signature)	Product Information
Field Copy Certification 21 CFR 314.94(d)(5) (original signature)	Summary of Product Characteristics, Labeling and Package Leaflet
Reference Details	**Reference Details**
Financial Certifications Bioavailability/Bioequivalence Financial Certification (Form FDA 3454) **-OR-** Disclosure Statement (Form FDA 3455)	Mock-up Specimen
Patent Information Patents listed for the RLD in the Electronic Orange Book Approved Drug Products with Therapeutic Equivalence Evaluations	Product Information already approved in the Member States
References Letters of Authorization 1. DMF letters of authorization a. Type II DMF authorization letter(s) or synthesis for Active Pharmaceutical Ingredient b. Type II DMF# c. Type III DMF authorization letter(s) for container closure d. Type III or V DMF authorization letter(s) for sterile	Braille Information about the Experts Quality Clinical

product sterilization process 2. US Agent Letter of Authorization (U.S. Agent [if needed, countersignature on 356h])	
Comparison between Generic Drug and RLD-505(j)(2)(A) 1. Conditions of use 2. Active ingredients 3. Inactive ingredients 4. Route of administration 5. Dosage Form 6. Strength	Specific Requirements for different types of applications Information for Generic, "Hybrid" or Bio-similar Applications
Environmental Impact Analysis Statement **(**cite 21CFR 25.31 and 25.15(d), if applicable)	Environmental risk assessment
Draft Labeling	Non-GMO & GMO

Table 2: Module 2 - Common Technical Document Summaries

In US	In Europe
CTD Introduction	Introduction
2.1 CTD table of contents	2.1 CTD table of contents
2.2 CTD introduction	2.2 CTD introduction
2.3 Quality Overall Summary	2.3 Quality Overall Summary
2.4 Non-clinical Overview	2.4 Non-clinical Overview
2.5 Clinical Overview - not required for generics	2.5 Clinical Overview - not required for generics
2.6 Non-clinical Summary – not required for generics	2.6 Non-clinical Summary – not required for generics
2.7 Clinical Summary	2.7 Clinical Summary
2.7.1 Summary of biopharmaceutics and associated analytical methods	2.7.1Summary of biopharmaceutics and associated analytical methods
2.7.2 Summary of clinical pharmacology studies	2.7.2 Summary of clinical pharmacology studies
2.7.3 Summary of clinical efficacy	2.7.3 Summary of clinical efficacy
2.7.4 Summary of clinical safety	2.7.4 Summary of clinical safety
2.7.5 Synopses of Individual Studies	2.7.5 Synopses of Individual Studies

Table 3: Module -3 (Quality)

IN US	IN EUROPE
3.1 TABLE OF CONTENTS	3.1 MODULE 3 TABLE OF CONTENTS
3.2 BODY OF DATA	3.2 BODY OF DATA
3.2.S DRUG SUBSTANCE	3.2.S DRUG SUBSTANCE
3.2.P Drug Product	In 3.2.S.2 Manufacture section, 3.2.S.2.3 to 3.2.S.2.6 is restricted part of ASMF
3.2.R REGIONAL INFORMATION (Drug Substance)	3.2.P Drug Product
3.2.R.1.S Executed Batch Records for drug substance (if available)	3.2.A APPENDICES
3.2.R.2.S Comparability Protocols	3.2.A.1Facilities and Equipment
3.2.R.3.S Methods Validation Package	3.2.A.2 Adventitious Agents Safety Evaluation
3.2.R REGIONAL INFORMATION (Drug Product)	3.2.A.3 Excipients
3.2.R.1.P.1 Executed Batch Records	3.2.R REGIONAL INFORMATION Validation of the process
3.2.R.1.P.2 Information on Components	3.3 LITERATURE REFERENCES
3.2.R.2.P Comparability Protocols	
3.2.R.3.P Methods Validation Package	

Module -4 non clinical study reports – for generics it is not applicable

Table 4: Module -5 Clinical Study Reports

IN US	IN EUROPE
5.1 module 5 table of contents of module	5.1 MODULE 5 TABLE OF CONTENTS
5.2 Tabular Listing of Clinical Studies	5.2 TABULAR LISTINGS OF ALL CLINICAL STUDIES
5.3 clinical study reports	5.3 CLINICAL STUDY REPORTS
5.3.1 reports of biopharmaceutics studies	5.3.1 Reports of Biopharmaceutical Studies
5.3.1.1 bioavailability (BA) study reports	5.3.2 Reports of Studies Pertinent to Pharmacokinetics
5.3.1.2 comparative BA and bioequivalence (BE) study reports	using Human Biomaterials
5.3.1.3 In vitro - in vivo correlation study reports	5.3.3 Reports of human pharmacokinetic(PK)studies
5.3.1.4 reports of bio analytical and analytical methods for human studies	5.3.4 Reports of human pharmacodynamic(PD)studies
5.4 literature references	5.3.5 Reports of efficacy and safety studies
	5.3.6 Reports of post-marketing experience
	5.3.7 Case report forms and individual patient listings, when submitted
	5.4 LITERATURE REFERENCES

Status of Generic Drugs

A numerical indication of number of generic drugs approved and number of generic drugs withdrawn post approval in the US (Figure. 6) and Europe (Figure. 7) was represented in the form of bar diagrams.

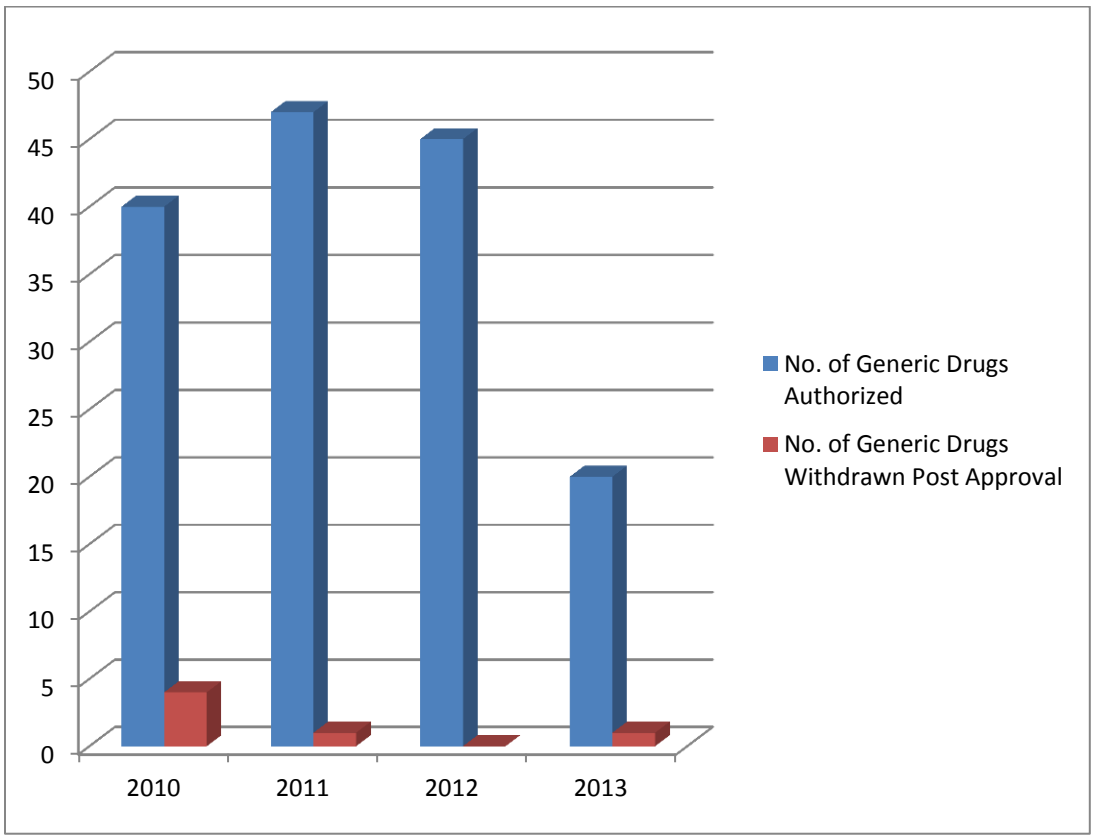

Figure. 6: Status of Generic Drugs in the US from 2010-2013

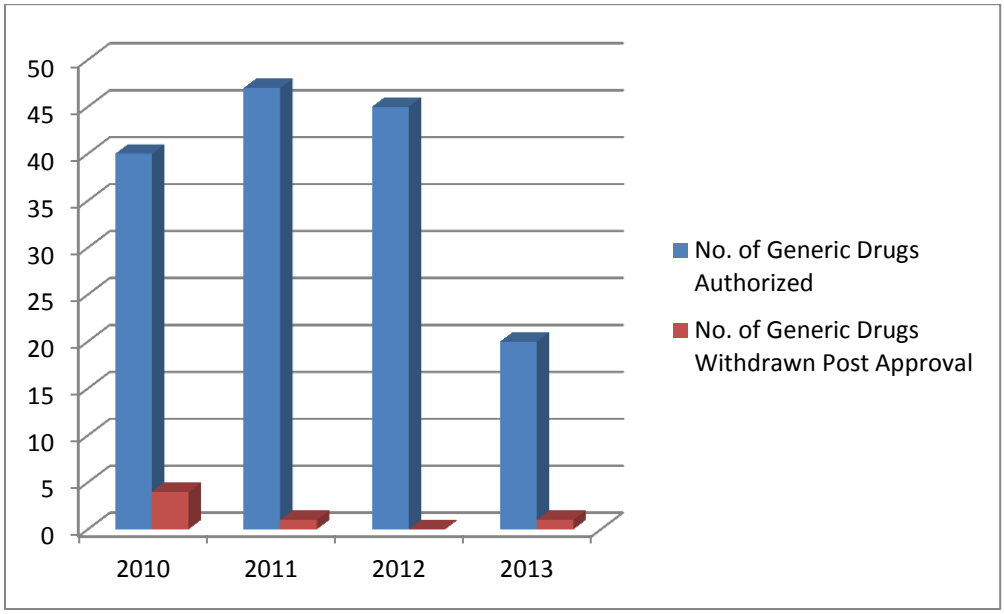

Figure. 7: Status of Generic Drugs in Europe from 2010-2013

CONCLUSION

In Europe, there is no central EU procedure for generic drug approval and one has to get approvals in each country by the national route. Countries have different standards; there are high registration costs and long timelines for registration of generic drugs. This may account for the low market share of generics in Europe as compared to USA [13]. Pharmaceutical markets of the USA and Europe together constitute lion's share of the global pharmaceutical market. So, there is an increased demand for generic drug approvals in these nations. The primary purpose of the rules governing medicinal products in US & Europe is to check whether drugs are manufactured in accordance to the guidelines so that they are safe and patient's well - being is protected. It is the role of public regulatory authorities to safe guard public health by ensuring that pharmaceutical companies comply with regulations so that safe and effective medications reach the market.

REFERENCES

1. Dylst P, Vulto A, Simoens S., Overcoming challenges in market access of generic medicines in the European Union. Journal of Generic Medicines 2012, 9, 21-8.
2. Hassali M, Shafie A, Awaisu A, Ibrahim M, Ping C, Jamshed S., Physicians' views on generic medicines: a narrative review. Journal of Generic Medicines 2010, 7, 30-9.
3. US Food and Drug Administration. New molecular entity approvals for 2012. US Food and Drug Administration

[http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugInnovation/ucm336115.htm] 2013.

4. Federal Food, Drug, and Cosmetic Act, 21 U.S.C. §§ 355(b)(2)(A)(i)-(iv) (2000).
5. Rick NG. Drugs from discovery to approval. 2nd ed. John Wiley & Sons, Inc., (Hoboken, New Jersey). p. 201-20.
6. The U.S. Drug Approval Process: A Primer [Internet]. [cited 2013 March] Available from: http://www.thememoryhole.org/crs/more-reports/RL30989.pdf
7. Garattini. L. Tediosi. F., A comparative analysis of generics markets in five European countries. Health Pol 2000, 51, 149–62.
8. The Centralised Procedure - European Commission [Internet]. [cited 2013 March] Available from: http//ec.europa.eu/health/authorisation-procedures-centralised_en. html.
9. Medicine and Healthcare Products Regulatory Agency, London [Internet]. [cited April 2014] Available from: http://www.mhra.gov.uk/Howweregulate/Medicines/Licensingofmedicines/Marketingauthorisations/Typesofapplication/index.htm
10. The Decentralized Procedure - European Commission [Internet]. [cited 2013 July] Available from: http//ec.europa.eu/health/authorisation-procedures-decentralised_en. html
11. The Mutual Recognition Procedure - European Commission [Internet].[cited 2013 May] Available from: http;//www.ec.europa.eu/health/authorisation-procedures-mutual-recognition_en. html.
12. NTA, Vol. 2B-CTD, foreword & introduction, edition June 2006 Available from: http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/homev2.htm
13. Simoens. S., Generic medicine pricing in Europe: Current issues and future perspective. J Med Econ 2008, 11, 171–5.