WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.074
Volume 7, Issue 16, 800-815. Research Article ISSN 2277– 7105

GENERIC DRUG REGISTRATION AND REGULATORY REQUIREMENTS IN EUROPEAN COUNTRIES

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Article Received on
22 June 2018,

Revised on 12 July 2018,
Accepted on 02 August 2018,

DOI: 10.20959/wjpr201816-13108

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ABSTRACT

The aim of this document is to examine methodological challenges by comparing generic drug registration and regulatory requirements in European countries. European countries are fast growing and emerging markets in pharmaceutical sector. Increasing patent expirations and the need for less expensive drugs is fuelling the growth of generics market in the region. However, there are some challenges to be met in order to sustain the growth. Hence the objective of present study is to analyse overall aspects like the requirements for registration of generics in the following 28 "EMA" (European medicines agency) countries, Drug registration procedure for the approval of generic drug in these countries, Mark out the differences in the requirements to register generic drug product in these countries. The primary purpose of the rules governing generic drugs in Europe is to safeguard to public health. It is the role of public regulatory authorities to ensure that pharmaceutical companies comply with regulations. There are legislations that require drugs to be developed, tested, trailed, and manufactured in accordance to the guidelines so that they are safe and patient's well - being is protected. The regulatory submissions in the EU, in the world continue to have significant differences. When compared to others the EU approval process is typical and contain more data to be summarized for the dossier submission.

KEYWORDS: Generic drug registration, Regulatory requirements, European medicines agency (EMA), European countries.

1. INTRODUCTION

GENERIC DRUGS

A generic drug (generic drugs, short: generics) is a drug defined as "a drug product that is comparable to a brand/reference listed drug product in dosage form, strength, quality and performance characteristics, and intended use.

Generic drugs are labeled with the name of the manufacturer and the adopted name (nonproprietary name) of the drug.

A generic drug must contain the same active ingredients as the original formulation. The generic drug have same rigid standards as the innovator drug.

- Contains the same active ingredients as the innovator drug
- Be identical in strength, dosage form, and route of administration
- Have the same use indications
- Be bioequivalence

Current Status of Generics in Europe

Europe, with its fast-growing, young population and uninsured majority represent great opportunity for generics in the pharmaceutical industry.

Flag of Europe

Generic market shares vary from country to country, presenting differing oppurtunities for generic manufacturers, see Figure 1, but in general are increasing across the regions. Increasing use of generics in the region is expected due to healthcare reforms – making drugs available to more of the population – and governmental cost-containment strategies. The expanding middle class is also expected to drive demand for medicines, and especially generics, in the region.

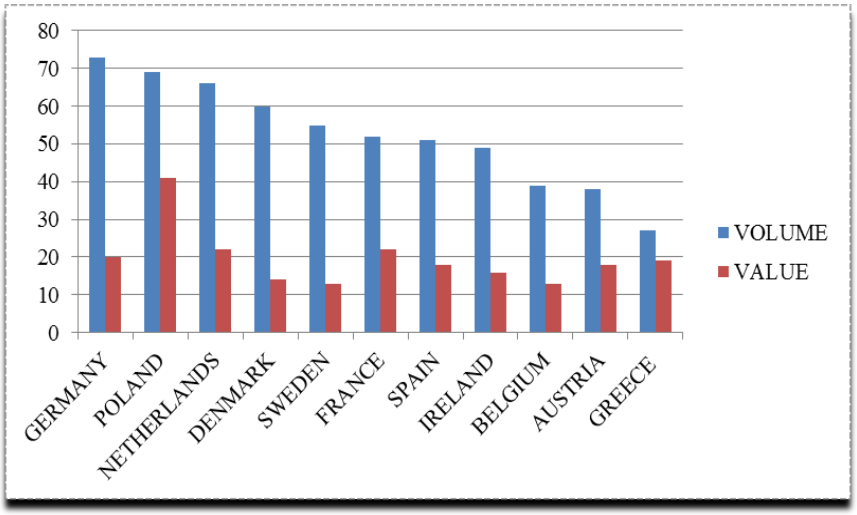


FIGURE 1: Generic market share in Selected European countries (2016).

GENERIC DRUG DEVELOPMENT

Pharmaceutical drug discovery and development has seen tremendous changes over the recent decades. A recent literature review concluded that medicines are among the most valuable forms of health care and are instrumental in treating various diseases more effectively. Generic medicines market shares differ substantially in Europe. Figure 2 provides an overview of the evolution of the market shares in ten European countries from June 2002 until March 2007. Figure 2(a) shows the evolution in five countries with high generic medicine market share (Denmark, Germany, the Netherlands, Sweden and UK) while Figure 2(b) shows the evolution in five countries with low generic medicine market share (Austria, Belgium, France, Italy and Spain). Generic medicine market shares have increased in all ten countries and this is due to the various political measures taken by governments.

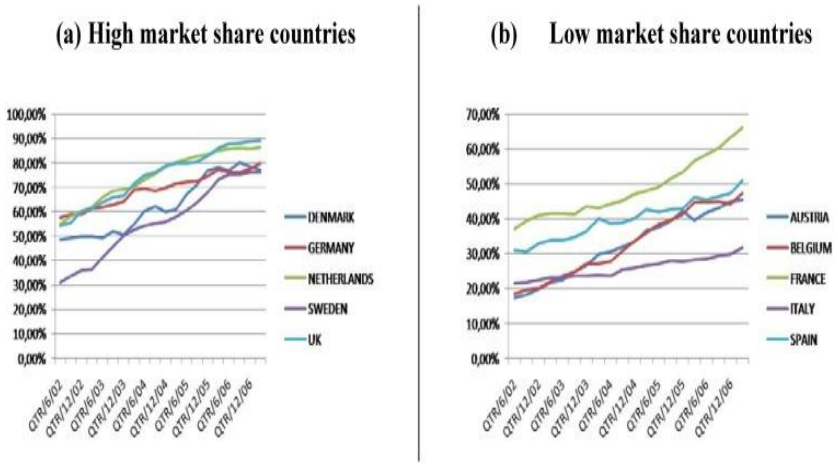


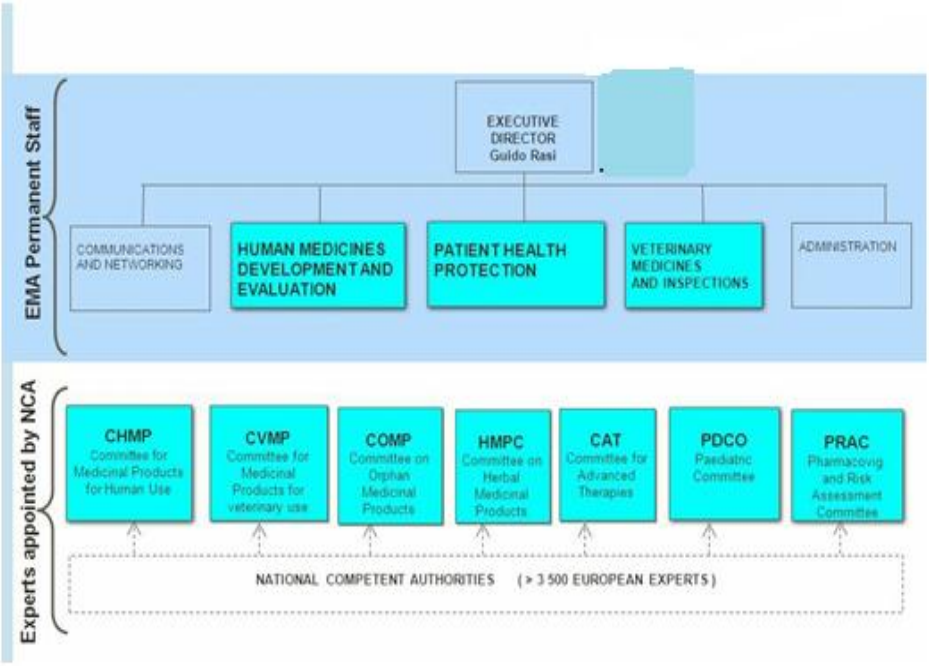
FIGURE 2: Evolution of Higher and Lower Generic Market Share in Five Countries.

INTRODUCTION TO EMA

The European Medicines Evaluation Agency (here after referred to as EMA) is a decentralised agency of the European Union (EU). The Management Board is the European Medicines Agency's integral governance body. The Agency is responsible for the scientific evaluation, supervision and safety monitoring of medicines developed by pharmaceutical companies for use in the EU. EMA protects public and animal health in 28 EU Member States, as well as the countries of the European Economic Area, by ensuring that all medicines available on the EU market are safe, effective and of high quality. EMA serves a market of over 500 million people living in the EU.

All parties are linked by an IT network EudraNet. (EUDRANET, the European TelecommunicationNetworkinPharmaceuticals (European Union Drug Regulating Authoritie s Network), is an IT platform to facilitate the exchange of information between regulatory partners and industry during submission and evaluation of applications).

Organization chart of the European Medicines Agency



ELECTRONIC COMMON TECHNICAL DOCUMENT (eCTD)

The European countries established the electronic common technical document (eCTD) as their format for submissions. It is a standard derived from ICH CTD. The eCTD is defined as an interface for industry to agency transfer of regulatory information while at the same time

taking into consideration the facilitation of the creation, review, lifecycle management and archival of the electronic submission.

STRUCTURE OF eCTD

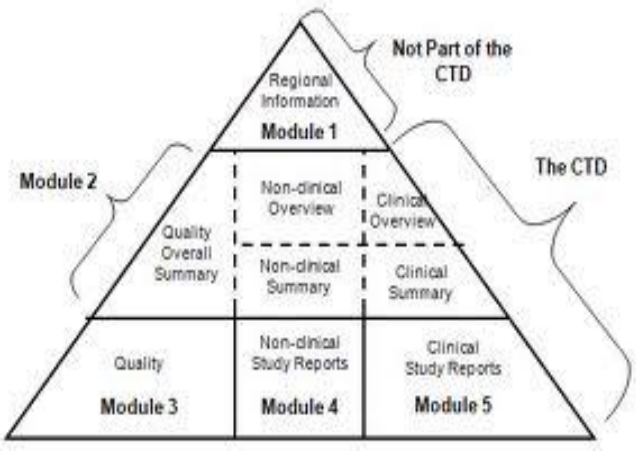


Figure 3: Structure of eCTD.

eCTD application

An eCTD application may comprise a number of sequences. In the EU an eCTD application may comprise several dosage forms and strengths, all under one invented product name. Some review tools describe such a collection as a dossier.

EGA (European Generic Medicine Association)

The EGA was established in 1993. The EGA is the official representative body of the European generic and biosimilar pharmaceutical industry, which is at the forefront of Providing high-quality affordable medicines to millions of Europeans and stimulating Competitiveness and innovation in the pharmaceutical sector.

Generic Drug Registration in Europe

Registration procedure of drugs in EU

- National Procedure
- Centralized Procedure
- Decentralized Procedure
- Mutual Recognition Procedure

Marketing Authorization based on approval received from above procedures

1. Repeat use application

2. Duplicate use application

Dossier requirements for generic drug application in Europe

The requirements for the dossier for the European countries are in principle very similar to requirements for the ICH countries.

Dossier for generic drug filling shall be submitted in the form of CTD in Europe. Generic Drugs are approved under MAA (Marketing Authorization Application).

Types of Applications

Generic Application – According to Article 10 (I) of Directive 2001/83/EC, the applicant is not required to provide the results of Pre clinical tests and Clinical tests if he can demonstrate that the medicinal product is a generic medicinal product of a reference medicinal product which is or has been authorized for not less than 8 years in a Member State or a Community.

A medicinal product is defined as a generic medicinal product if it has –

- The same qualitative and quantitative composition in active substance as that of reference product.
- The same pharmaceutical form as the reference product.
- And whose Bio-equivalence with the reference medicinal product has been Demonstrated with appropriate Bio-availability studies.

2. SCOPE OF THE STUDY

European countries are fast growing and emerging markets in pharmaceutical sector. Increasing patent expirations and the need for less expensive drugs is fuelling the growth of generics market in the region. However, there are some challenges to be met in order to sustain the growth. Hence the objective of present study is to analyze overall aspects about:

- The requirements for registration of generics in the following 28 “EMA” (European medicines agency) countries.
- Drug registration procedure for the approval of generic drug in these countries.
- Mark out the differences in the requirements to register genric drug product in these countries.

3. METHODOLOGY

The dissertation work was done in order to project industrial approach in facilitating pharmaceutical company's entry into the market of European countries.

Criteria for selection of study parameters

As the generic drug registration in European countries is a sequential process, four parameters are selected for the understanding the regulatory registration and requirements

Part 1: Requirement for filing application

Part 2: Documents and study information required for submission

Part 3: Product registration and dossier submission

Part 4: Comparison study

4. RESULTS

Table 1: General Comparsion of Selected European Countries.

S. No.	Country	Ma status	Validity	Sunset clause for 3 years	Format followed	Renewal for every 5 years	Format included in thesis
1	**Germany**	Granted	5 years	If granted	eCTD	Not needed	eCTD
2	**Poland**	Granted	5 years	If granted	eCTD	Not needed	eCTD
3	**Netherlands**	Granted	5 years	If granted	eCTD	Not needed	eCTD
4	**Denmark**	Granted	5 years	If granted	eCTD	Not needed	eCTD
5	**Sweden**	Granted	5 years	If granted	eCTD	Not needed	eCTD
6	**France**	Granted	5 years	If granted	eCTD	Not needed	eCTD
7	**Spain**	Granted	5 years	If granted	eCTD	Not needed	eCTD
8	**Ireland**	Granted	5 years	If granted	eCTD	Not needed	eCTD
9	**Ausrtia**	Granted	5 years	If granted	eCTD	Not needed	eCTD
10	**Greece**	Granted	5 years	If granted	eCTD	Not needed	eCTD

Table 2: Generic Drug Dossier Submission in Europe.

Requirements	Europe
Agency	Multiple Agencies • EMEA • CHMP • National Health Agencies
Registration Process	Multiple Registration Process •Centralized (Europea Community) • Decentralized (At least 2 member states) • Mutual Recognition (At least 2 member states) • National (1 member state)
TSE / BSE Study data	TSE / BSE Study data required

Application	MAA
Stability data	The stability data for accelerated studies are submitted for complete 6 months at the time of original Submission.
Approval time	12 months
Pharmacopeias	BP/Ph. Eur
Process Validation	required
Braille code	Braille code is required on labelling
Post approval changes	Post variation in the approved drug Type 1A variation Type 1B variation Type II variation

Table 3: Administrative Requirements in Europe.

S. No.	Requirement	Europe
1	Application	MAA
2	Debarment classification	Not required
3	Number of copies	1
4	Approval Timeline	12 months
5	Fees	10-20 lakhs
6	Presentation	eCTD

Table 4: Finished Product Control Requirements in Europe.

S. No.	Requirement	EU
1	Justification	ICH Q6A
2	Assay	95-105%
3	Disintegration	Required
4	Color Identification	Required
5	Water Content	Not required

Table 5: Manufacturing & Control Requirements in Europe.

S. No.	Requirement	EU
1	Number of batches	3
2	Packaging	Required
3	Process Validation	Required
4	Batch Size	Minimum of 1,00,000 Units

Table 6: Stability Requirements in Europe.

S. No.	Requirement	EU
1	Number of batches	**2**
2	Condition	25/60 - 40/75
3	Date & Time of Submission	6 Months Accelerate & 6 Months long term
4	Container orientation	Do not address
5	Clause	Vol 4 EU Guidelines for medicinal products
6	QP Certification	Required

Table 7: Bioequivalence Requirements in Europe.

S. No.	Requirement	EU
1	CRO	Audited by MHRA
2	Reserve Sample	No such requirement
3	Fasted / Fed	No such requirement
4	Retention of samples	No such requirement

Table 8: Documents Comparsion of Selected European Countries.

S. No.	Administrative Documents	Germany	Poland	Denmark	Sweden	Spain	Ireland	Greece
1	Application form	√	√	√	√	√	√	√
2	Audit certificate	√	√	√	√	√	√	√
3	Import licence	√	√	√	√	√	√	√
4	Power of attorney	√	√	√	√	√	√	√
5	Testing site	√	√	√	√	√	√	√
6	eGMP compliance	√	√	√	√	√	√	√
7	Manufacture for sale Form-25	√	√	√	√	√	√	√
8	Process flow chart indicating different sites involved in manufacturing and releasing	√	√	√	√	√	√	√
9	Certificate of GMP compliance and manufacturing	√	√	√	√	√	√	√
10	Manufacturer GMP	√	√	√	√	√	√	√
11	Qualified person declaration concerning GMP compilace	√	√	√	√	√	√	√
12	Labelling documents	√	√	√	√	√	√	√
13	Patent information leaflet	√	√	√	√	√	√	√
14	BE requirements	√	√	√	√	√	√	√

5. DISCUSSION

Generic Drug Registration And Requirements In All Valid European Union

There are four different registration procedures (marketing authorization procedures) for generic drugs in all valid European union. There are two regulatory steps to go through before a drug is approved to be marketed in the European Union. These two steps are clinical trial application and marketing authorization application. The European Medicines Agency (EMA) is responsible for the scientific evaluation of centralized marketing

authorization applications (MAA). Once granted by the European Commission, the centralized marketing authorization is valid in all European Union (EU) Member States, Iceland, Norway and Liechtenstein.

Procedures for application for a marketing authorization

Centralized procedure

National procedure

Mutual recognition procedure

Decentralized procedure

Centralized Procedure (CP)

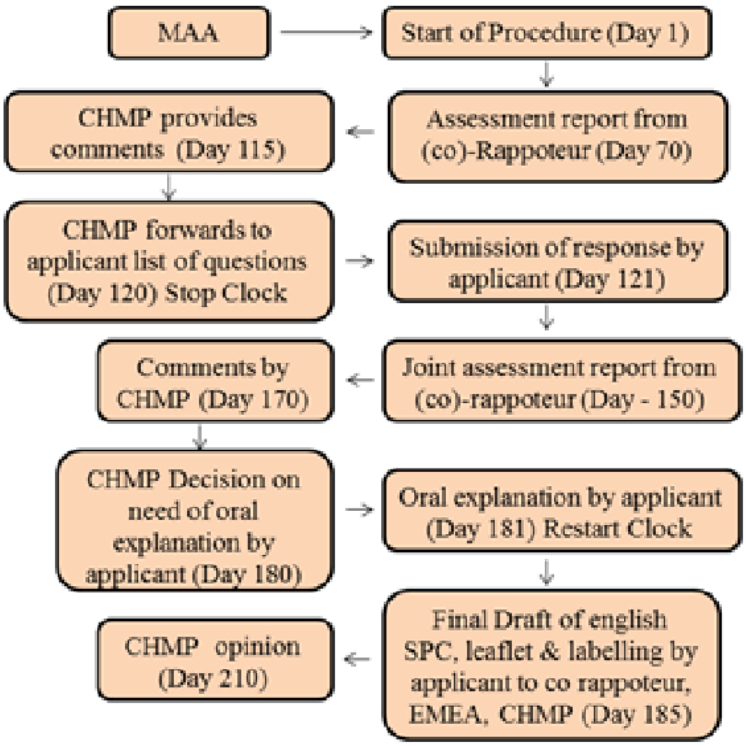


Figure 4: Summary of Centralized Procedure.

National Procedure (NP)

Generally, this procedure is no longer used nowadays. If an applicant wishes to obtain a license in one Member State (MS) an application must be made to the national Competent Authority (CA) which then issues a national license. With the exception of products granted a marketing authorization under the centralized procedure as set out above, all products are granted marketing authorizations on a country-by-country basis by the competent authorities in each Member State. Such marketing authorizations permit the holder to market the product

in question in the Member State concerned, subject to any restrictions or requirements that accompany the authorization.

Mutual Recognition Procedure (MRP)

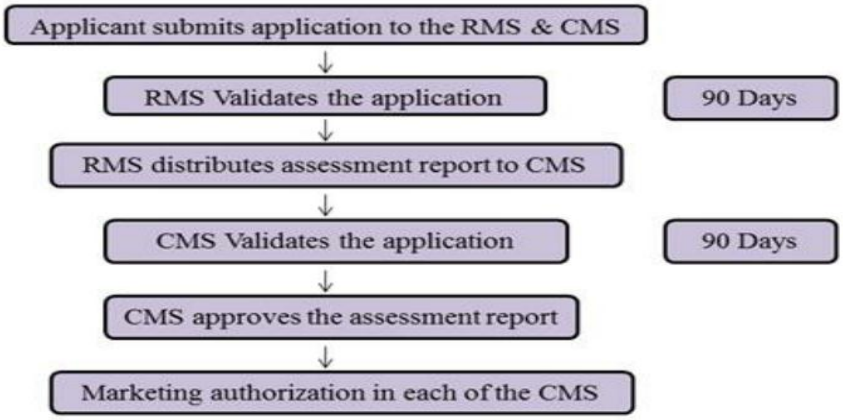


Figure 5: Summary of Mutual recognition procedure.

Decentralized procedure (DCP)

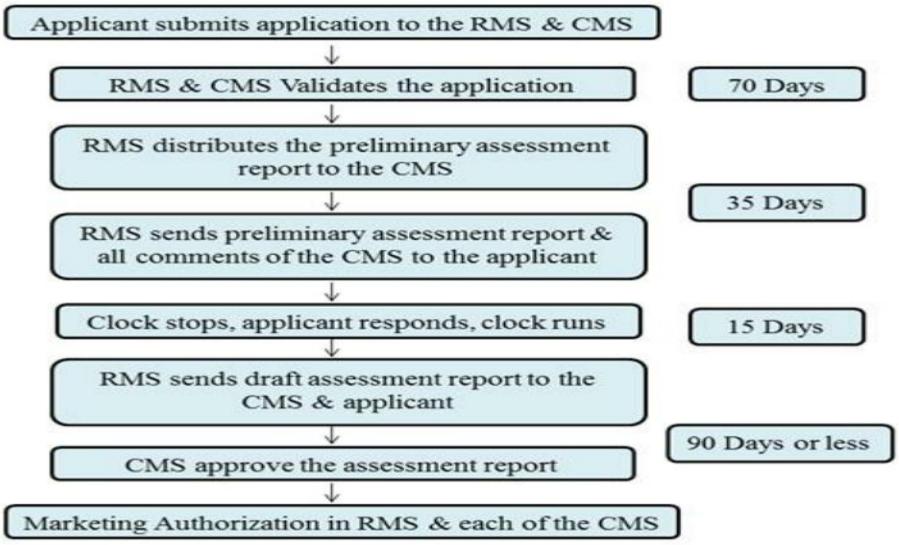


Figure 6: Summary of Decentralized procedure.

Table 9: Summary of European marketing application options.

Process	When used	Pros	Cons
National authorization	Individual application to each country within the EU. Used for products that fall outside the scope of the EMA centralized procedure	If application rejected in one country, can still access other Europe countries	Separate application required for each country. Unique requirements and formats may be required
Decentralized procedure	Used for products that fall outside the scope of the EMA centralized procedure.	Simultaneous authorization in numerous countries in the EU. May be more efficient than national authorization since a positive outcome results in numerous country approvals. Sponsors can select which countries to apply to;does not have to be all EU countries	A negative decision on an application may affect numerous countries.
Mutual recognition procedure	Individual application to one country which in the EU for products that fall outside the scope of the EMA centralized procedure	Review by one country and other countries accept the decision. Only one application needs to be submitted.	Individual national approvals can add significant time to the process. A negative outcome can effect numerous countries.
Centralized procedure	Used for biological products or other products using high technology procedures; products for HIV/AIDS, cancer, diabetes, autoimmune or dysfunction, and viral diseases, product for orphan conditions;and other new active substance at the request of the applicant.	One application applies to all countries in the EU. Relatively quick procedure. A positive outcome is very beneficial to the sponsor.	A negative outcome will affect access to the entire EU.

Procedures for obtaining a marketing authorization

Authorization processes follow either a purely national procedure, with rules and requirements as per national legislation in force, as it occurs in most of countries worldwide, or should follow a centrally approval or a mutual recognition or decentralized procedure within the European Union.

Steps involved in obtaining an EU marketing authorization

Submission of eligibility request

⇩

Notification of intention to submit an application

⇩

Appointment of rapporteurs

⇩

Pre-submission meeting

⇩

Reconfirmation of communicated submission date

⇩

Submission and validation of application

⇩

Scientific evaluation

⇩

CHMP scientific opinion

⇩

European commission decision

Dossier to be submitted

The EMEA requires from the applicant: One full copy of the dossier (modules 1-5 according to the EU-CTD format), including the applicant's part of the Active Substance Master File, if any; ¬ Two additional copies of Modules 1 and 2 including the draft summary of product characteristics, labelling and package leaflet in English; ¬ One electronic copy of module 1 and 2 (at least 2.1-2.5) in WORD. In addition, applicants must submit the dossier to both the Rapporteur and the Co-Rapporteur in parallel to the EMEA. Otherwise there may be a delay in the start of the procedure because of the time lapse between the validation by the EMEA and the confirmation from the Rapporteur and the Co-Rapporteur that they have received the dossiers.

Validation by the EMA

During validation the EMA Product Team Lead (PTL) consults the Rapporteur and Co-Rapporteur, on the need for action relating to matters such as GMP inspection, ad-hoc expert groups, Scientific Advisory Groups, GCP inspections, and completeness of data.

Positive outcome of the validation

Negative outcome of the validation

Types of applications

The type of application may vary according to status of the active ingredient.

Thus, if the application concerns a new active ingredient (new active substance, new chemical entity, new molecular entity), one talks about a full application.

Generic Application – According to Article 10 (I) of Directive 2001/83/EC, the applicant is not required to provide the results of Pre clinical tests and Clinical tests if he can demonstrate that the medicinal product is a generic medicinal product of a reference medicinal product which is or has been authorized for not less than 8 years in a Member State or a Community.

A medicinal product is defined as a generic medicinal product if it has:

- The same qualitative and quantitative composition in active substance as that of reference product.
- The same pharmaceutical form as the reference product.
- And whose Bio-equivalence with the reference medicinal product has been demonstrated with appropriate Bio-availability studies.

6. CONCLUSION

The primary purpose of the rules governing generic drugs in Europe is to safeguard to public health. It is the role of public regulatory authorities to ensure that pharmaceutical companies comply with regulations. There are legislations that require drugs to be developed, tested, trailed, and manufactured in accordance to the guidelines so that they are safe and patient's well - being is protected. The regulatory submissions in the EU, in the world continue to have significant differences. When compared to others the EU approval process is typical and contain more data to be summarized for the dossier submission. All OECD countries see the development of generic markets as a good opportunity to increase efficiency in pharmaceutical spending but many do not fully exploit the potential of generics. Some of the differences in generic uptake can be explained by market structures, notably the number of off-patent medicines, and by prescribing practices, but generic uptake also very much depends on policies implemented by countries. It also compares the registration procedure, regulatory pathways for the registration of drugs in EU. The EU requires to select from any one of the marketing authorization procedure.

To succeed with multinational registrations, a sponsor must:

- Identify key target markets for submissions.
- Understand important regional differences.
- Find the right local resources to avoid regulatory pitfalls.
- Create a robust CTD (Common Technical Document).

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