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A PROCESSION AT THE EU REGULATORY GUIDELINES

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Abstract:

In this retrospective study which deals about the rules & regulations which are required for drug approval process in Europe. Developing a new drug requires great amount of research work in pharmaceutical sciences and pharmacological basics. Drug reviewers in regulatory agencies around the world bear the responsibility of evaluating whether the research data support the safety, effectiveness and quality control. Every country has its own regulatory authority, which is responsible to enforce the rules and regulations and issue the guidelines to regulate the marketing of the drugs. This retrospective provides clear information on list of EU member countries, EEA, EFTA, and EMA. Different types of submission procedure for regulatory approvals were explained clearly. The European Medicines Agency is responsible for the centralized authorization procedure for human and veterinary medicines. This procedure results in a single marketing authorization that is valid in all EU countries, as well as in the European Economic Area (EEA) countries. The regulatory strategy for product development is essentially to be established before commencement of developmental work in order to avoid major surprises after submission of the application. The role of the regulatory authorities is to ensure the quality, safety, and efficacy of all medicines in circulation in their country.

***Key Words**: EU – European Union, EMA – European Medical Agency, EEA - European Economic Area.*

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INTRODUCTION:

The EU has one of the most highly regarded regulatory systems in the world. The system comprises of European parliament, the council of ministers, and the European Commission. EU consists of 27 member states: Austria, Belgium, Bulgaria, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Luxemburg, Malta, Netherlands, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden, and the United Kingdom and three countries which are member of European Free Trade Agreement (EFTA) Iceland, Norway, and Liechtenstein. These EFTA members are those countries which were unable to join rest of the 27 member states as common market. These three EFTA member countries along with 27 EU member states, comprises of the European Economic Area (EEA). The European Medicines Agency is a decentralized agency of the European Union, located in London. The Agency is responsible for the scientific evaluation of medicines developed by pharmaceutical companies for use in the European Union and applications for European marketing authorizations for both human and veterinary medicines (centralized procedure). Under the centralized procedure, companies submit a single marketing-authorization application to the Agency. Once granted by the European Commission, a centralized (or "Community") marketing authorization is valid in all European Union (EU) and EEA-EFTA states (Iceland, Liechtenstein and Norway). The European parliament approves the laws together with the council of ministers. The council of ministers is the voice of Member states and is responsible for enactment of directives. [1]

The ideas formed from the basic scientific research enter into translational research, which is concerned with efficiently moving basic discoveries from concept into clinical evaluation, often focused on specific disease entities or therapeutic concepts [2]. The European Medicines Agency (EMEA) was formed in 1995 and is based in London, England. The EMEA coordinates the existing scientific resources of the Member States for the evaluation, supervision, and pharmacovigilance of medicinal products for both human and veterinary use throughout the EU [3]. The signing of confidentiality arrangements in September 2003 has increased the level of cooperation between the EMEA and the FDA, particularly in the provision of parallel scientific advice to companies developing new medicines [4].

Types of submission procedure

To market a generic medicinal product in European Economic Area (EEA) which consists of 27 member states and 3 EFTA countries, a marketing authorization has to be issued. European medicines Agency (EMA formerly known as EMEA) regulates the medicinal products marketing authorization through various committees. Different types of submissions for receiving Marketing authorization in Europe are given below in [1]

Table 1: European Union member countries & Non-European union member countries [5]

Sl.No	*European Union member countries*	*Non-European union member countries*
1.	Austria	Iceland *
2.	Belgium	Norway *
3.	Bulgaria	Switzerland
4.	Cyprus	Serbia
5.	Czech Republic	Montenegro
6.	Denmark	Croatia
7.	Estonia	Bosnia-Herzegovina
8.	Finland	Macedonia (Former Republic of Yugoslav)
9.	France	Albania
10.	Germany	Andorra
11.	Greece	Belarus
12.	Hungary	Moldova

Continue…

13.	Ireland	Monaco *
14.	Italy	San Marino
15.	Latvia	Liechtenstein *
16.	Lithuania	Vatican City
17.	Luxembourg	Russia
18.	Malta	Ukraine
19.	Netherlands	Georgia
20.	Poland	
21.	Portugal	
22.	Romania	
23.	Slovakia	
24.	Slovenia	
25.	Spain	
26.	Sweden	
27.	United Kingdom	

New EU System uses two Drug Approval Procedures

Under the new EU drug approval process, pharmaceutical companies may use either a centralized or a decentralized procedure to obtain approval to market their pharmaceutical products in more than one Member State using one application. These procedures modify the former multistate and concentration procedures by (1) defining specific review steps and establishing time limits for review processes and (5) requiring Member States to accept as binding, decisions that are issued by the Commission. In addition, the CPMP, which was formally an advisory arm of the Commission, now serves as one of the EMEA's scientific committees. The CPMP, composed of two representatives from each Member State, renders opinions about the safety, efficacy, and quality of human pharmaceutical products that are binding on all the Member States. Although the new EU drug approval process changes the method for obtaining a marketing authorization, it does not affect drug pricing and reimbursement policies, which remain the responsibility of each Member State. Thus, in order to actually market a pharmaceutical product approved under the new process, manufacturers must still negotiate a product's price with individual Member States. [6]

The role of the European Medicines Agency

The EMA is responsible for the scientific evaluation, primarily of innovative and high technology medicines developed by pharmaceutical companies for use in the EU. The EMA was set up to ensure the best use of scientific resources across Europe.

Experts participate in the work of the EMA as members of its scientific committees, working parties, scientific advisory groups and other ad hoc advisory groups, or as members of the assessment teams carrying out the evaluation of medicines.

Experts are chosen on the basis of their scientific expertise and are mostly made available to the EMA by the medicines regulatory authorities in Member States. Increasingly, patients and healthcare professionals are involved in the work of the EMA. [7]

The EMA's scientific committees

The EMA has seven scientific committees that carry out its scientific assessments: [7]

• Committee for Medicinal Products for Human Use
• Pharmacovigilance Risk Assessment Committee
• Committee for Medicinal Products for Veterinary Use
• Committee for Orphan Medicinal Products
• Committee on Herbal Medicinal Products
• Committee for Advanced Therapies
• Paediatric Committee

DRUG APPROVAL PROCESS IN EUROPE:

The European Medicines Evaluation Agency (EMEA) was established in London, in the year 1995, to coordinate the European Union (EU) member states for evaluating and supervising the

medicinal products for both human and veterinary use. It introduced a transparent procedure for the development, consultation, finalization and implementation of pharmaceutical guidelines.

Medicinal products are widely regulated in Europe to safeguard public health, and to facilitate access of European patients to innovative drugs [3]

The drug approval process in European countries is accomplished in two phases: 1. Clinical trial; 2. Marketing authorization. A clinical trial application (CTA) is filed to the competent authority of the state to conduct the clinical trial within European Union (EU). The competent authority of that member state evaluates the application. The clinical trials are conducted only after the approval. Marketing authorization application is filed only after all the three phases of clinical trials are completed. [8]

The European Legislation containing the pharmaceutical directives has been published in the following volumes entitled The Rules Governing Medicinal Products in the European Union [8]

Volume 1 - Pharmaceutical Legislation for Medicinal Products for human use.

Volume 2 - Notice to Applicants for Medicinal Products for human use.
Volume 3 - Scientific Guidelines for Medicinal Products for human use
Volume 4 - Good Manufacturing Practices Guidelines for Medicinal Products for human and veterinary use
Volume 5 - Pharmaceutical Legislation for Medicinal Products for veterinary use
Volume 6 - Notice to Applicants for Medicinal Products for veterinary use.
Volume 7 - Scientific Guidelines for Medicinal Products for veterinary use
Volume 8 - Maximum Residue Limits
Volume 9 - Pharmaco-vigilance Guidelines for Medicinal Products for human and veterinary use
Volume 10 - Clinical Trials Guidelines.

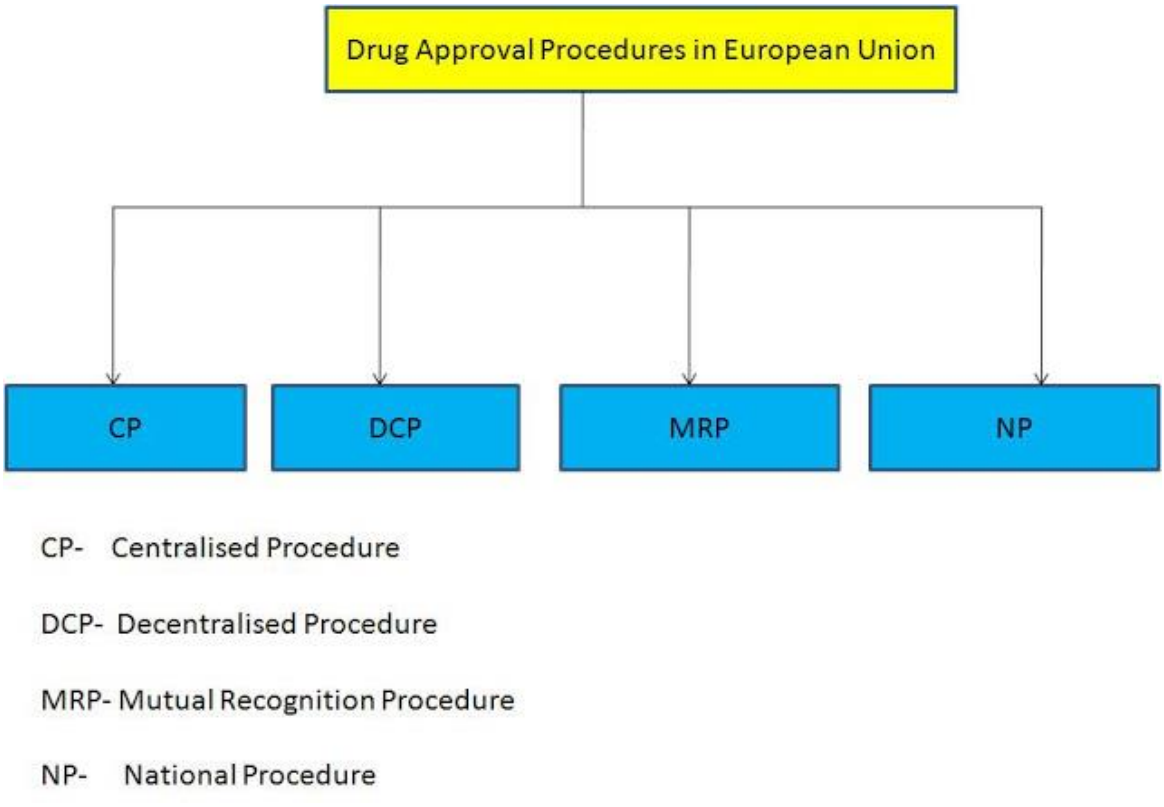

Fig 1: Flow chart of Drug approval Procedures in Europe Union [2]

Centralized Procedure

Allows a pharmaceutical company to market its pharmaceutical product in all 25 member states without having to obtain separate approvals from each member state. [9]

Decentralized Procedure

An applicant can go directly to a national marketing authority to obtain permission to market its product in that member state and then seek to have other member states accept the marketing approval of the first member state. Mutual recognition procedure (MRP)- Used in order to obtain marketing authorizations in several Member States where the medicinal product in question has received a marketing authorization in at least one Member State at the time of application. [9]

Mutual Recognition Procedure

This procedure is similar to the de-centralized procedure. This procedure is applicable to medicinal products which have received a marketing authorization in any member state whereas the decentralized procedure is applicable to those products which were never approved in any member states of the European Union. This procedure is open for all drug types except biotechnology products. The submission can be made to any number of the other member states and the Reference Member State sends a copy of the assessment report to the Concerned Member States's, who can raise any objections within 90 days. Each Concerned Member States issues a national marketing authorization with an identical Summary of Product Characteristics. [8]

National Procedure

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 authorisation under the centralised procedure as set out above, all products are granted marketing authorisations on a country-by-country basis by the competent authorities in each Member State. Such marketing authorisations permit the holder to market the product in question in the Member State concerned, subject to any restrictions or requirements that accompany the authorization. [10]

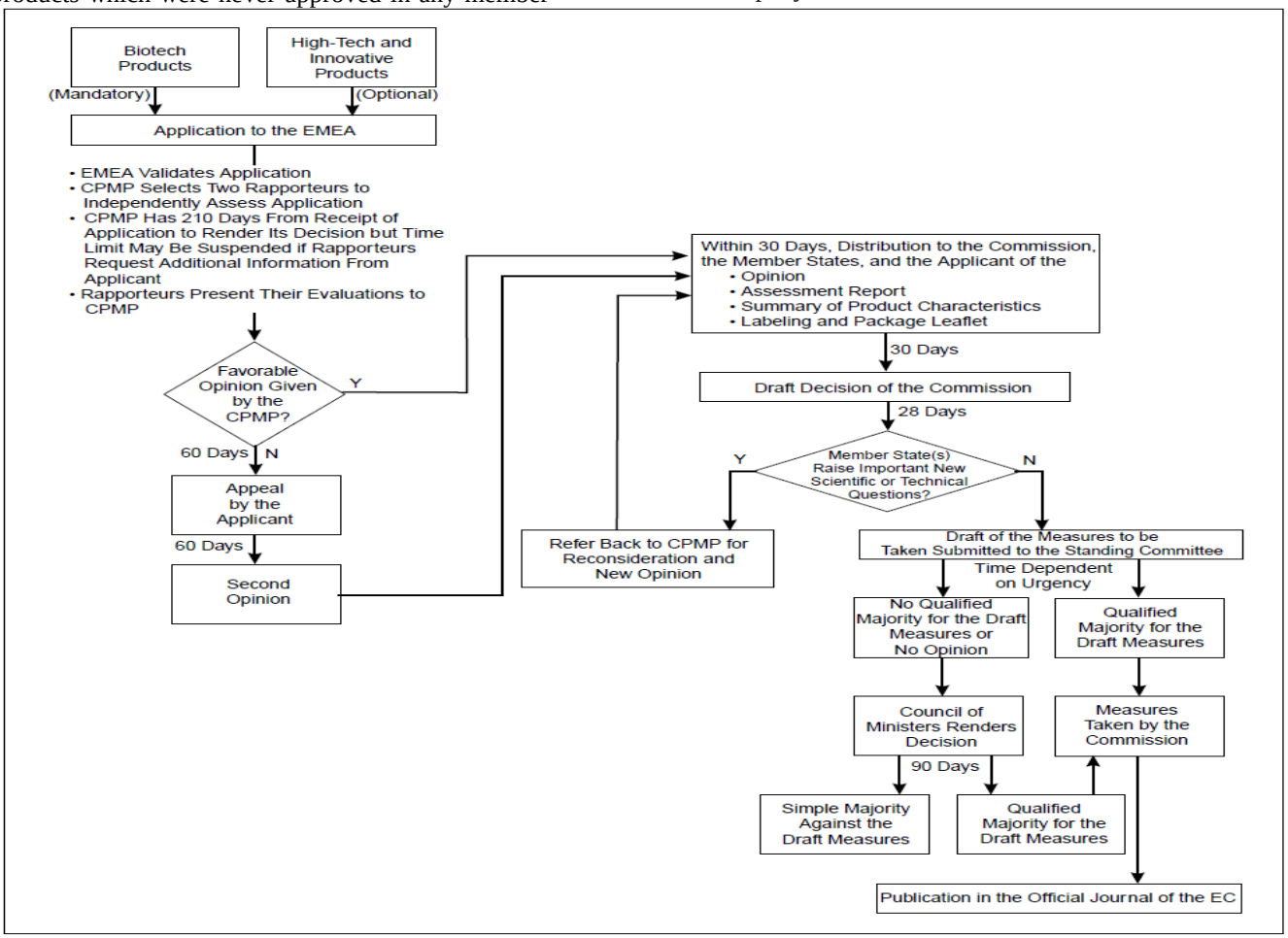

Fig 2: Flow chart of Centralized Procedure [6]

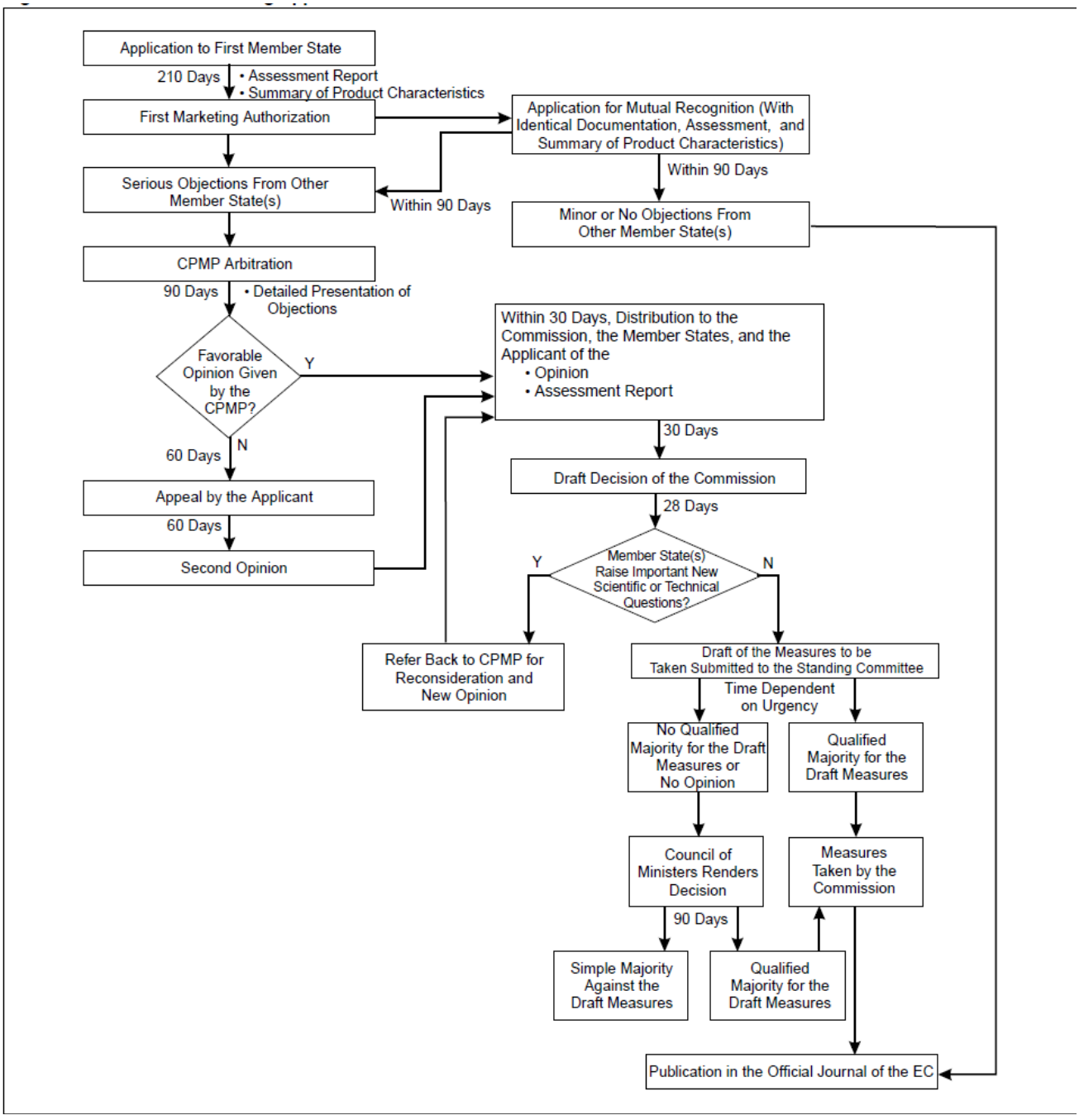

Fig 3: Flow chart of Decentralized Procedure [6]

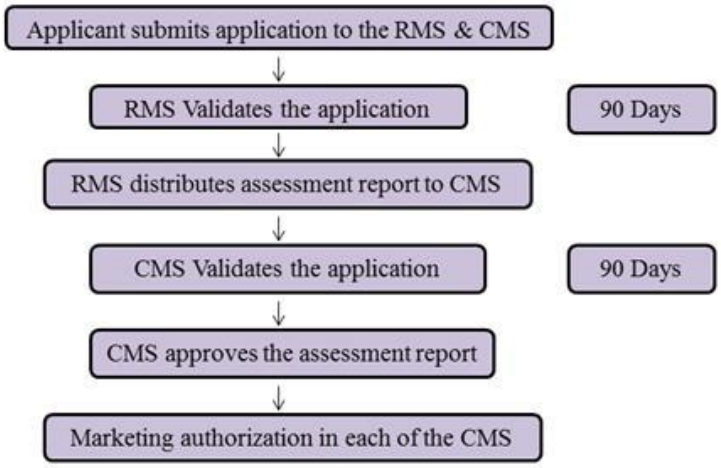

Fig 4: Flow chart of Mutual Recognition Procedure [11]

Table 2: Country wise Regulatory Agencies [12]

Sl.No	Country	Name of the Regulatory Agencies
1.	Austria	Austrian Agency for Health and Food Safety
2.	Belgium	Federal Agency for Medicines and Health Products
3.	Bulgaria	Bulgarian Drug Agency
4.	Croatia	Agency for medicinal products and medical devices of Croatia
5.	Cyprus	Ministry of Health - Pharmaceutical Services
6.	Czech Republic	State Institute for Drug Control

7.	Denmark	Danish Health and Medicines Authority
8.	Estonia	State Agency of Medicines
9.	Finland	Finnish Medicines Agency
10.	France	National Agency for the Safety of Medicine and Health Products
11.	Germany	Federal Institute for Drugs and Medical Devices
12.	Germany	Paul Ehrlich Institute
13.	Greece	National Organization for Medicines
14.	Hungary	National Institute of Pharmacy
15.	Iceland	Icelandic Medicines Agency
16.	Ireland	Health Products Regulatory Authority (HPRA)

17.	Italy	Italian Medicines Agency
18.	Latvia	State Agency of Medicines
19.	Liechtenstein	Office of Health / Department of Pharmaceuticals
20.	Lithuania	State Medicines Control Agency
21.	Luxembourg	Ministry of Health
22.	Malta	Medicines Authority
23.	Netherlands	Medicines Evaluation Board
24.	Netherlands	Healthcare Inspectorate
25.	Norway	Norwegian Medicines Agency
26.	Poland	Office for Registration of Medicinal Products, Medical Devices and Biocidal Products

27.	Poland	Main Pharmaceutical Inspectorate
28.	Portugal	National Authority of Medicines and Health Products
29.	Romania	National Medicines Agency
30.	Slovakia	State Institute for Drug Control
31.	Slovenia	Agency for Medicinal Products and Medical Devices of the Republic of Slovenia
32.	Spain	Spanish Agency for Medicines and Health Products
33.	Sweden	Medical Products Agency
34.	United Kingdom	Medicines and Healthcare Products Regulatory Agency

Table 3: Principles of EU [13]

Sl.no	Requirements	EU
1.	Agency	**Multiple Agencies** ➢ EMEA ➢ CHMP ➢ National Health Agencies
2.	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)
3.	TSE/BSE Study data	TSE/BSE Study data required
4.	Braille code	Braille code is required on labelling
5.	Post-approval changes	**Post-variation in the approved drug:** ➢ Type IA Variation ➢ Type IB Variation ➢ Type II Variation

Table 4: Administrative Requirements [13]

Sl.no	Requirements	EU
1.	Application	MAA
2.	Debarment classification	Not Required
3.	Number of copies	1
4.	Approval Timeline	~12 Months
5.	Fees	National fee (including hybrid applications): £103,059 Decentralized procedure where UK is CMS: £99,507
6.	Presentation	eCTD

Table 5: Finished Product Control Requirements [13]

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

Table 6: Manufacturing & Control Requirements [13]

S.No	Requirements	EU
1.	Number of batches	3
2.	Packaging	Not Required
3.	Process Validation	Required
4.	Batch Size	2 pilot scale plus 1 lab batch or minimum of 1 lakh units whichever is higher.

Table 7: Stability Requirements [13]

Sl.no	Requirements	EU
1.	Number of batches	2 Pilot Scale (If API Stable) 3 Primary Batches (If API unstable)
2.	Condition: Long term stability, Accelerated stability	Long term: 25°C/60%RH Accelerated: 40°C/75%RH(0,3,6 months) Intermediate: 30°C/65%RH
3.	Minimum time period at Submission	6 Months Accelerate & 6 Months long term
4.	Container orientation	Do not address
5.	Clause	Volume 4 EU Guidelines for medicinal products
6.	QP Certification	Required

Table 8: Bioequivalence Requirements [13]

Sl.no	Requirements	EU
1.	CRO (Audits)	Audited by MHRA
2.	Reserve Sample	No such requirement
3.	Fasted / Fed	No such requirement
4.	Retention of samples	No such requirement
5.	BE study for generic drugs	Against EU reference product (ERP) in any country

CONCLUSION:

In EU there is increased emphasis on comparisons between the new agent and existing agents. However, in the current system where pharmaceutical companies frequently conduct a clinical program for submission in all regions, the main clinical requirement would be to demonstrate efficacy and safety. The evaluation of a new medicinal product of chemical or biologic origin is considered by Health Authorities as a process that requires the highest guarantee of quality, efficacy, and safety. The EU has developed a regulatory system to facilitate cooperation among the Member States and the EMEA plays a prominent role.

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