CHAPTER

3

Marketing authorization and licensing of medicinal products in EU: Regulatory aspects

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1. Introduction

The EU market represented by its 27 Member States (plus Norway, Iceland, and Liechtenstein) and possibly the United Kingdom (pending negotiations on Brexit) is very large in size and pharmaceutical companies from around the world find it very lucrative to penetrate, observing the rules governing licensing medicinal products in the EU.

From EU perspectives, it is imperative that these medicinal products are of the quality and standard to be considered safe and efficacious from the time of manufacture and over their shelf life.

Also, it is imperative that medicinal products are prescribed and dispensed in line with the indication(s) approved along with their safety profiles being transparent to the public and consumers.

These rules and guidelines would cover licensing and regulation of manufacturing sites, quality of the drug substance as an active ingredient, quality of the drug product manufactured, and the drug product's release in the market. Also, they would cover the indication(s) approved, side effects reported, legal status and presentations, as well as follow-up issues while in the market.

From the applicant perspective, the procedures followed and compliance with the requirements are crucial, dictating the strategy of marketing of the medicinal product in the concerned Member States and level of penetration envisaged.

In this chapter, the governing bodies in the EU and their role, the legal framework, and rules regulating the entrance of the medicinal product and licensing in the EU is explained. Whilst focus on the human medicinal products will be made; however, and wherever appropriate the committees and groups that govern the licensing of veterinary medicines will be mentioned.

In general, the same documents may apply for both types of medicinal products unless they are specifically mentioned.

While covering the main concepts and requirements for licensing and marketing of medicinal products in the EU, discussion of licensing

Drug Delivery Trends
https://doi.org/10.1016/B978-0-12-817870-6.00003-1

medicinal products containing chemical entities of the drug substance is primarily made, but does not cover biologicals. In most cases, different rules would apply, which are beyond the aim of this chapter.

Furthermore, pharmacovigilance regulations and guidelines, though part of the licensing requirements, are beyond the aim of this chapter and will not be covered.

Procedures for referrals and tribunals, when no consensus among all concerned Member States involved in the application can be agreed in the initial process of assessment and timelines, are covered.

Also, the role and responsibility of the marketing authorization holder (MAH) to ensure compliance with the rules in effect at the time of submission and throughout the lifecycle of the product while it is licensed will be explained.

In addition to the EU guidelines, compliance with national rules in drawing the strategy of marketing and sale of the medicinal product in the concerned Member State would have to be carefully considered.

In this respect it is important to highlight that although all EU Member States are obliged to abide by EU rules, they still have their own national rules that need to be considered and a difference in the requirements between these two rules is possible.

As an aid for better understanding, hyperlinks to the main websites are given when possible.

2. European Union legal framework, hierarchy, and committees

In this section the legal entities and committees of the European Medicines Agency (EMA), the hierarchy within the EU, and the process of decision-making are explained. This is of importance due to direct involvement of the EMA (via its different committees) in drawing the policy of the Agency, governing the process of marketing authorization of medicinal products in the EU, publishing guidelines, as well as reviewing and deciding on referred cases when synonymous decisions within the different Member States cannot be reached.

The following is the hierarchy of the EU and linkage to the EMA as depicted in Fig. 3.1.

2.1 The European Union

The EU is a politico-economic union of 27 (after Brexit) Member States that are located primarily in Europe. The EU operates through a system of supranational institutions and intergovernmental-negotiated decisions by the Member States.

It has an area of 4,475,757 km^2 (1,728,099 sq mi) and an estimated population of over 510 million. The EU has developed an internal single market through a standardized system of laws that apply in all Member States.

2.2 The European commission [1]

This is the EU's executive arm. It makes decisions on the Union's political and strategic direction. The Commission is steered by a group of 27 (after Brexit) Commissioners, known as "the college." Together they make decisions on the Commission's political and strategic direction.

2.3 Departments and agencies [2]

The Commission is organized into policy departments, known as Directorates-General (DGs), which are responsible for different policy areas. DGs develop, implement, and manage EU policy, law, and funding programs. In addition, service departments deal with particular administrative issues. Executive agencies manage programs set up by the Commission.

2.4 Consumers, health, agriculture and food executive agency [3]

This executive agency of the Commission manages EU programs on consumer rights, health, agriculture, and safe food.

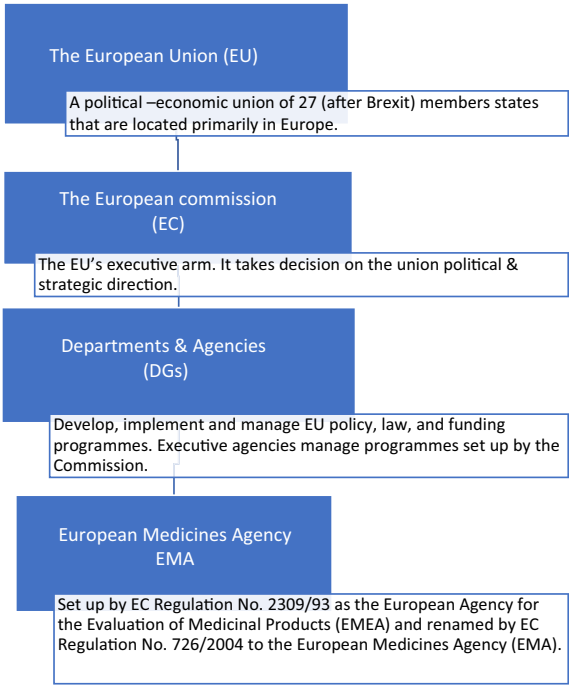

FIGURE 3.1 Hierarchy of the European Union and linkage to the European Medicines Agency.

2.5 Health and food safety department [4]

This Commission department is responsible for EU policy on food safety and health and for monitoring the implementation of related laws.

2.6 European medicines agency [5]

The EMA was set up by European Commission (EC) Regulation No. 2309/93 as the European Agency for the Evaluation of Medicinal Products and renamed by EC Regulation No. 726/2004 to the European Medicines Agency.

The EMA is a decentralized agency of the European Union. It began operating in 1995 relocated from London to Amsterdam/The Netherlands on March 29, 2019.

The Agency is responsible for the scientific evaluation, supervision, and safety monitoring of medicines in the EU.

The EMA protects public and animal health in the EU Member States, as well as the countries of the European Economic Area (EEA), by ensuring that all medicines available on the EU market are safe, effective, and of high quality.

The EMA serves a market of over 500 million people living in the EU

The organizational plan of the EMA is presented in Fig. 3.2.

The EMA has seven scientific committees and several working parties and related groups, which conduct the scientific work of the Agency.

The working parties and groups are made up of members who have expertise in a particular scientific field, selected from the list of European experts maintained by the Agency. Members are given tasks associated with the scientific evaluation of marketing authorization applications or drafting and revision of scientific guidance documents.

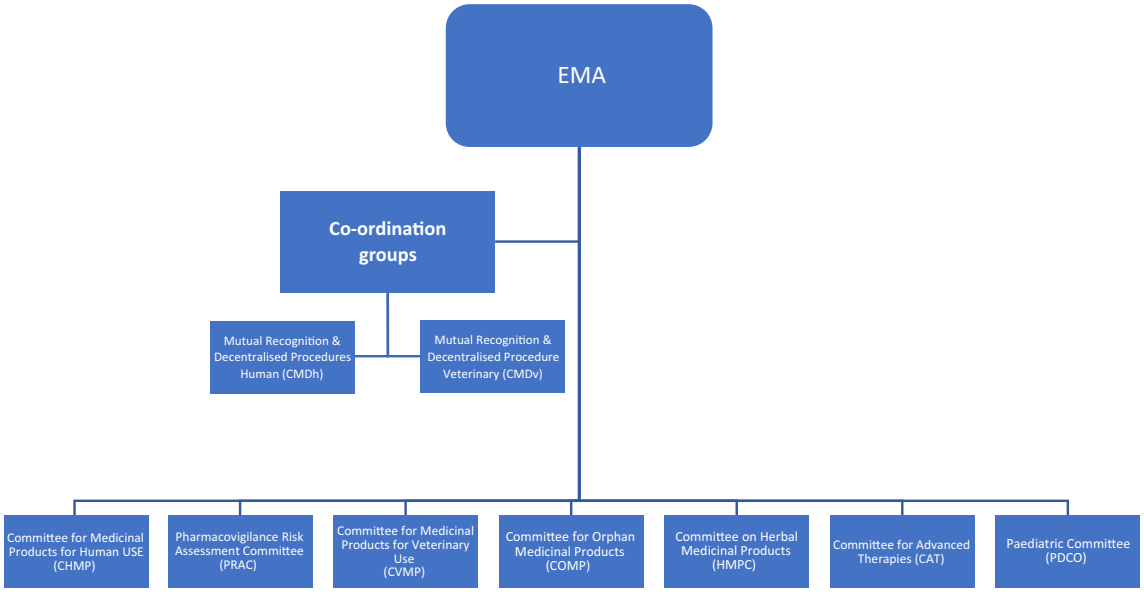

FIGURE 3.2 Hierarchy of the European Medicines Agency whereby each committee has a working party.

The following is a brief description of each of the EMA committees, their roles and responsibilities as well as standing working parties linked to each committee.

For more about other committees-associated groups, readers are advised to visit the main website of the EMA/committees.

2.6.1 *Committee for medicinal products for human use* [6]

This is the EMA's committee responsible for human medicines.

2.6.1.1 Role

The Committee for Medicinal Products for Human Use (CHMP) plays a vital role in the authorization of medicines in the EU.

In the centralized procedure, the CHMP is responsible for:

- Conducting the initial assessment of EU-wide marketing authorization applications
- Assessing modifications or extensions ("variations") to an existing marketing authorization
- Considering the recommendations of the Agency's Pharmacovigilance Risk Assessment Committee (PRAC) on the safety of medicines on the market and when necessary recommending to the EC changes to a medicine's marketing authorization, or its suspension or withdrawal from the market
- Evaluating medicines authorized at national level referred to the EMA for a harmonized position across the EU. For more information, see union referral procedures discussed in section 2 of this chapter

The current CHMP standing working parties are:

- Healthcare Professionals' Working Party
- Biologics Working Party
- Patients' and Consumers' Working Party
- Quality Working Party
- Safety Working Party
- Scientific Advice Working Party

The CHMP is further supported by the work of the Good Manufacturing Practice, Good Clinical Practice, and Good Laboratory Practice Inspection Services Groups. Information on their role is available on the EMA website.

2.6.2 *Pharmacovigilance risk assessment committee* [7]

This is the EMA's committee responsible for assessing and monitoring the safety of human medicines.

The PRAC was formally established in line with the pharmacovigilance legislation, which came into effect in 2012 to help strengthen the safety monitoring of medicines across Europe.

2.6.2.1 Role

The PRAC is responsible for assessing all aspects of risk management of human medicines, including:

- The detection, assessment, minimization, and communication of the risk of adverse reactions, while taking the therapeutic effect of the medicine into account;
- Design and evaluation of post-authorization safety studies;
- Pharmacovigilance audit.

The PRAC provides recommendations on questions on pharmacovigilance and risk management systems, including the monitoring of their effectiveness, to the:

- CHMP for centrally authorized medicines and referral procedures;
- Coordination Group for Mutual Recognition and Decentralised Procedures—Human (CMDh) on the use of a medicine in Member States;
- The EMA secretariat, Management Board, and EC, as applicable.

By virtue of the nature of the PRAC, there are no working parties or groups attached to it.

2.6.3 *Committee for medicinal products for veterinary use* [8]

This is the EMA's committee responsible for veterinary medicines, established in line with Regulation (EC) No. 726/2004.

2.6.3.1 Role

The Committee for Medicinal Products for Veterinary Use (CVMP) plays a vital role in the authorization of veterinary medicines in the EU.

In the centralized procedure, the CVMP is responsible for:

- Conducting the initial assessment of EU-wide marketing authorization applications;
- Postauthorization and maintenance activities, including the assessment of any modifications or extensions ("variations") to an existing marketing authorization;
- Safety monitoring of veterinary medicines on the market and when necessary recommending to the EC changes to a medicine's marketing authorization, or its suspension or withdrawal from the market. For more information, see veterinary pharmacovigilance given in the EMA website.

The CVMP also evaluates veterinary medicines authorized at national level referred to the EMA for a harmonized position across the EU. For more information, see veterinary referral procedures given in the EMA website.

The CVMP recommends safe limits for residues of veterinary medicines used in food-producing animals and biocidal products used in animal husbandry for the establishment of maximum residue limits by the EC.

In addition, the CVMP and its working parties contribute to the development of veterinary medicines and medicine regulation by:

- Providing scientific advice to companies researching and developing new veterinary medicines;

- Preparing scientific guidelines and regulatory guidance to help pharmaceutical companies prepare marketing authorization applications for veterinary medicines;
- Cooperating with international partners on the harmonization of regulatory requirements.

2.6.3.1.1 Assessments

The CVMP's assessments are based on a comprehensive scientific evaluation of data. They determine whether the medicine meets the necessary quality, safety, and efficacy requirements and that is has a positive risk/benefit balance in favor of the animal population they are intended for.

A peer-review system safeguards the accuracy and validity of the opinions of the committee.

The current CVMP working parties are:

- Antimicrobials Working Party
- Efficacy Working Party
- Environmental Risk Assessment Working Party
- Immunologicals Working Party
- Quality Working Party
- Pharmacovigilance Working Party
- Safety Working Party
- Scientific Advice Working Party

The CVMP is further supported by the work of the Good Manufacturing Practice Inspection Services Group. Information on its role is available on the EMA website.

2.6.4 Committee for Orphan Medicinal Products [9]

This is the EMA's committee responsible for recommending orphan designation of medicines for rare diseases, established in 2000, in line with Regulation (EC) No. 141/2000.

2.6.4.1 Role

The Committee for Orphan Medicinal Products (COMP) is responsible for evaluating applications for orphan designation for human use. This designation is for medicines to be developed for the diagnosis, prevention, or treatment of rare diseases that are life threatening or very serious. In the EU, a disease is defined as rare if it affects fewer than 5 in 10,000 people across the EU. The EC decides whether to grant an orphan designation for the medicine based on the COMP's opinion.

An orphan designation allows a pharmaceutical company to benefit from incentives from the EU, such as reduced fees and protection from competition once the medicine is placed on the market.

The COMP also advises and assists the EC on matters related to orphan medicines, including:

- Developing and establishing an EU-wide policy;
- Drawing up detailed guidelines;
- Liaising internationally.

The current COMP working party is: Patients' and Consumers' Working Party.

2.6.5 Committee on herbal medicinal products [10]

This is the EMA's committee responsible for compiling and assessing scientific data on herbal substances, preparations, and combinations to support the harmonization of the European market.

The Committee on Herbal Medicinal Products (HMPC) replaced the Committee for Proprietary Medicinal Products' Working Party on Herbal Medicinal Products in September 2004. The Committee was established in accordance with Regulation (EC) No. 726/2004 and the Herbal Directive, which introduced a simplified registration procedure for traditional herbal medicinal products in EU Member States.

The HMPC is composed of scientific experts in the field of herbal medicines.

2.6.5.1 Role

The HMPC prepares the Agency's opinions on herbal substances and preparations, along with information on recommended uses and safe conditions.

This work supports the harmonization of the European market: national competent authorities are able to refer to one unique set of information on an herbal substance or preparation when evaluating marketing applications for herbal medicines.

To support EU Member States, the HMPC focuses on two main tasks:

- Establishing EU monographs covering the therapeutic uses and safe conditions of well-established and/or traditional use for herbal substances and preparations;
- Drafting an EU list of herbal substances, preparations, and combinations thereof for use in traditional herbal medicinal products.

The HMPC and its working parties and other groups also:

- Prepare scientific guidelines and regulatory guidance to help companies prepare marketing authorization and registration applications for herbal medicines;
- Prepare opinions on questions referred to the EMA by the national competent authorities regarding the period and evidence of safe use for traditional herbal medicinal products;
- Cooperate with the European Directorate for the Quality of Medicines and Healthcare on European Pharmacopoeia standards and EMA guidance on the quality of herbal medicines;
- Coordinate with other scientific committees at the Agency on the regulation and safe use of herbal medicines;
- Provide scientific and regulatory support to companies researching and developing herbal medicines;
- Interact with interested parties;
- Provide advice and training to herbal assessors of national competent authorities;
- Cooperate with international partners on the harmonization of regulatory requirements.

The current HMPC working parties are:

- Working Party on European Union Monographs and European Union List
- Patients' and Consumers' Working Party

The HMPC is further supported by the work of the Good Manufacturing Practice Inspection Services Group. Information on its role is available on the EMA website.

2.6.6 *Committee for advanced therapies [11]*

This is the EMA's committee responsible for assessing the quality, safety, and efficacy of advanced therapy medicinal products (ATMPs) and following scientific developments in the field.

It was established in accordance with Regulation (EC) No. 1394/2007 on ATMPs as a multidisciplinary committee, gathering some of the best available experts in Europe.

2.6.6.1 Role

The committee's main responsibility is to prepare a draft opinion on each ATMP application submitted to the EMA before the CHMP adopts a final opinion on the marketing authorization of the medicine concerned.

At the request of the EMA's Executive Director or the EC, the Committee for Advanced Therapies (CAT) can also draw up an opinion on any scientific matter relating to ATMPs.

The CAT also:

- Participates in certifying quality and nonclinical data for small and medium-sized enterprises developing ATMPs;

- Participates in providing scientific recommendations on the classification of ATMPs;
- Contributes to scientific advice in cooperation with the Scientific Advice Working Party;
- Takes part in any procedure delivering advice on the conduct of efficacy follow-up, pharmacovigilance, or risk-management systems for ATMPs;
- Advises the CHMP on any medicinal product that may require expertise in ATMPs for the evaluation of its quality, safety, or efficacy;
- Assists scientifically in developing any documents relating to the objectives of the Regulation on ATMPs;
- Provides scientific expertise and advice for any Community initiative related to the development of innovative medicines and therapies that requires expertise on ATMPs;
- Supports the work programs of the CHMP working parties.

The CAT's work plan includes developing guidance documents, contributing to cross-committee projects, work on simplification of procedures and requirements for ATMPs, training for assessors, and organizing scientific workshops.

The current CAT associated group is:

- EMA/CAT and Medical Devices' Notified Body Collaboration Group

2.6.7 *Paediatric committee [12]*

This is the EMA's scientific committee responsible for activities on medicines for children and to support the development of such medicines in the EU by providing scientific expertise and defining paediatric needs.

The Paediatric Committee (PDCO) was established in line with the Paediatric Regulation, which came into effect in 2007, to improve the health of children in Europe by facilitating the development and availability of medicines for children aged 0–17 years.

2.6.7.1 Role

The PDCO's main role is to assess the content of paediatric investigation plans (PIPs), which determine the studies that companies must carry out in children when developing a medicine. This includes assessing applications for a full or partial waiver and for deferrals.

The committee's other roles include:

- Assessing data generated in accordance with agreed PIPs;
- Adopting opinions on the quality, safety, or efficacy of a medicine for use in the paediatric population, at the request of the CHMP or a medicines regulatory authority in an EU Member State. The PDCO can give an opinion if the data have been generated in accordance with an agreed PIP;
- Advising Member States on the content and format of data to be collected through surveys on the uses of medicines in children;
- Advising and supporting the development of the European Network of Paediatric Research at the EMA;
- Providing advice on questions on paediatric medicines, at the request of the Agency's Executive Director or the EC;
- Establishing and regularly updating an inventory of paediatric medicine needs;
- Advising the Agency and the EC on how to communicate the arrangements available for conducting research into paediatric medicines.

The PDCO is not responsible for marketing authorization applications for medicines for use in children, which is in the remit of the CHMP.

The current PDCO working groups are:

- Formulation Working Group
- Non-clinical Working Group
- Modelling and Simulation Working Group

2.7 Coordination groups

2.7.1 *Coordination group for mutual recognition and decentralised procedures—human* [13]

CMDh was set up in 2005. It replaced the informal Mutual Recognition Facilitation Group.

The CMDh examines questions relating to the marketing authorization of human medicines in two or more EU Member States in accordance with the mutual recognition or the decentralized procedures and questions concerning variations of these marketing authorizations.

If there is disagreement between Member States during the assessment of the submitted data based on the grounds of a potential serious risk to public health, the CMDh considers the matter and strives to reach an agreement within 60 days. If this is not possible, the Member State responsible for the product brings the case to the attention of the CHMP for arbitration.

The CMDh examines questions concerning the safety of noncentrally authorized medicines marketed in the EU where centrally authorized products are not affected. This includes adopting a CMDh position on safety-related EU referral procedures, taking account of the recommendations of the PRAC.

Each year the CMDh identifies a list of medicines for which harmonized product information should be drawn up, to promote the harmonization of marketing authorizations across the EU.

More information about the CMDh activities, including a complete overview of its functions and tasks, can be found on the CMDh website.

2.7.2 *Composition*

The CMDh is composed of one representative per Member State (plus Norway, Iceland, and Liechtenstein), appointed for a renewable period of 3 years. Member States may also appoint an alternate member, and observers from the EC and EU accession countries also participate in meetings. Information on the members and alternates of the CMDh is available on the CMDh website.

The EMA provides the secretariat to the CMDh.

2.7.3 *Meetings and reports*

The CMDh holds monthly meetings at the EMA lasting 3 days. After each meeting, the CMDh publishes a meeting report in the form of a press release.

The CMDh press releases are available on the CMDh website.

2.7.4 *Safety referrals*

The CMDh positions adopted in the context of safety-related referral procedures are currently published on the EMA website. Once a CMDh position is adopted, the EMA also publishes a press release summarizing the CMDh position.

The CMDh website contains further information on the CMDh and its work, including statistics, guidance documents, question-and-answer documents, work plans, annual reports, and information on the applications referred to the CMDh.

Similar description, composition, and responsibilities lie with the Coordination Group for Mutual Recognition and Decentralised Procedures—Veterinary [14].

3. Legal framework for licensing medicines for human use in the EU

3.1 Introduction

The EU legal framework guarantees high standards of quality and safety of medicinal products, while promoting the good functioning of the internal market with measures that encourage innovation and competitiveness.

It is mainly composed of Directives and Regulations published by the EC.

In this section, description of the regulatory requirements and rules governing the marketing

authorization of medicinal products for human use in the EU, the legal framework of the process of their licensing, procedures to be followed (depending on type of medicinal product to be licensed and marketing policy of the applicant), as well as other related topics are briefly explained.

Readers who are interested in veterinary medicines are referred to the main website of the EMA for further details.

While every effort has been made to maintain enough clarity on this very pronged and difficult to follow subject, dragging the reader into deeper details causing distraction from the main points covered in this section has been best avoided.

However, for further details of any of the topics discussed, the interested reader can review the original publications referred to in this section.

The following is a presentation of the most relevant legislations concerning authorization for marketing medicinal products in the EU.

3.2 Directive 2001/83/EC [15]

Since its publication in 2001, the Directive (2001/83/EC) has gone through a number of amendments, the latest of which was on November 16, 2012.

While the reader is strongly encouraged to familiarize him/herself with the Directive in general, and with the definitions given under Article 1 in particular, it is beyond the scope of this chapter to discuss the whole Directive in detail but to focus only on the main articles that are directly related to the licensing and marketing authorization of medicinal products in the EU.

3.2.1 *Article 6*

> No medicinal product may be placed on the market of a Member State unless a marketing authorisation has been issued by the competent authorities of that Member State in accordance with this Directive.

Also, under Article 6(1a) it is stated that the MAH shall be responsible for marketing the medicinal product and the designation of a representative shall not relieve the MAH of his/her legal responsibility.

It is paramount for the pharmaceutical companies to familiarize themselves with the requirements of licensing medicinal products in the EU and rules governing the process.

3.2.2 *Article 8(3)(i)*

Meeting the requirements of Article 6 is set under this article whereby results of the following studies are to be submitted:

- Pharmaceutical (physicochemical, biological, or microbiological) tests;
- Preclinical (toxicological and pharmacological) tests;
- Clinical trials.

Also, under Article 8(3)(ia), submission of a detailed description of the pharmacovigilance and, where appropriate, of the risk-management system that the applicant will introduce is to be made.

3.2.3 *Article 10.1*

For generic medicines:

> the applicant shall not be required to provide the results of pre-clinical tests and of clinical trials if he can demonstrate that the medicinal product is a generic of a reference medicinal product which is or has been authorised under Article 6 for not less than eight years in a Member State or in the Community.

Under the same article, the generic product cannot be placed on the market until 10 years have elapsed from the initial authorization of the reference product.

The exclusivity of 10 years granted to the reference product can be extended to a maximum of 11 years if, during the first 8 years of those 10 years, the MAH obtains an authorization for one more new therapeutic indication.

3.2.4 Article 10.3

In cases where the medicinal product:

1. Does not fall within the definition of a generic medicinal product as provided in Article 10(2), paragraph (b) of the Directive.
2. Or where the bioequivalence cannot be demonstrated through bioavailability studies;
3. Or in case of changes in the active substance(s), therapeutic indications, strength, pharmaceutical form or route of administration, vis-à-vis the reference medicinal product;

the results of the appropriate preclinical tests or clinical trials shall be provided.

3.2.5 Article 10a

> The applicant shall not be required to provide the results of pre-clinical tests or clinical trials if he can demonstrate that the active substances of the medicinal product have been in well-established medicinal use within the Community for at least ten years, with recognised efficacy and an acceptable level of safety in terms of the conditions set out in the Annex. In that event, the test and trial results shall be replaced by appropriate scientific literature.

3.2.6 Article 10b

> In the case of medicinal products containing active substances used in the composition of authorised medicinal products but not hitherto used in combination for therapeutic purposes, the results of new preclinical tests or new clinical trials relating to that combination shall be provided in accordance with Article 8(3)(i), but it shall not be necessary to provide scientific references relating to each individual active substance.

This article is about combination products of two actives or more with the requirements for preclinical tests and clinical trials.

There is always confusion between the requirements of this article and Article 10a. In other words, having a combination of two actives used for more than 10 years in the Community would not justify their application under 10a but should under Article 10b. The reason behind this is that the combination has not been in use in the Community in accordance with the requirements of Article 10a and safety and efficacy of the new combination should be assured as per Article 8(3)(i). However, if the combination has already been used for more than 10 years for the proposed indication, Article 10a would apply.

3.2.7 Article 10c

> Following the granting of a marketing authorisation, the authorisation holder may allow use to be made of the pharmaceutical, preclinical and clinical documentation contained in the file on the medicinal product, with a view to examining subsequent applications relating to other medicinal products possessing the same qualitative and quantitative composition in terms of active substances and the same pharmaceutical form.

The meaning of this article is to allow the MAH to have more than one license of the same product issued either to the same company or to another company that holds a consent from the original MAH.

This article is only applicable to reference products and not to generics.

3.3 Regulation (EC) No. 726/2004 [16]

The purpose of this regulation is to lay down Community procedures for authorization and supervision of medicinal products for human and veterinary use.

This has undergone many amendments since it was first published in 2004, the latest of which was on June 5, 2013.

It provides insight into the main articles of Directive 2001/83/EC as amended. Reference to this regulation will be made during the discussions of the different procedures adopted in the EU, avoiding repetition while focusing on the main points of interest.

3.4 EudraLex [17]

This is a collection of rules and regulations governing the marketing authorization of medicinal products in the EU defined by Directive 2001/83/EU as amended. It consists of 10 volumes.

Concerning medicinal products for human use, they are:

- Volume 1: Pharmaceutical Legislation
- Volume 2: Notice to Applicants
- Volume 3: Guidelines
- Volume 4: Good Manufacturing Practices
- Volume 9: Pharmacovigilance
- Volume 10: Clinical Trials

Volume 1 covers the pharmaceutical legislations concerning the authorization of medicinal products for human and veterinary use in the EU to include published Directives and Regulations. It provides access to the list of all the legislations and their history. Interested readers can access this volume by logging into EudraLex website given under reference no.17.

Volumes 5, 6, 7, and 8 as well as Volumes 4 and 9 concern veterinary medicinal products.

Volume 3 is no longer covered in EudraLex and referral to the EMA website is made.

Of direct interest, Volume 2 (Notice to Applicants) has been prepared in accordance with Article 6 of Regulation (EC) No. 726/2004 and Annex I of Directive 2001/83/EC on the Community Code relating to medicinal products for human use. It is intended to facilitate the interpretation and application of the Union pharmaceutical legislation and is composed of three subvolumes:

- Volume 2A deals with the procedure for marketing authorization.
- Volume 2B deals with the presentation and content of the dossier.
- Volume 2C deals with regulatory guidelines.

Each subvolume contains a number of chapters. Volume 2A is composed of six chapters:

- Chapter 1 Marketing Authorization—updated June 2018
- Chapter 2 Mutual Recognition—updated February 2007
- Chapter 3 Union Referral Procedures—updated December 2016
- Chapter 4 Centralised Procedure—deleted in July 2005 replaced by the website of the EMA
- Chapter 5 Variation Guidelines—May 2013
- Chapter 6 Community Marketing Authorisation—updated November 2005

For the purpose of this section, focus on Chapter 1 only will be made. It provides a summary of the subjects covered in other chapters, highlighting the main points and applications that are of interest.

For further details of any of the material discussed, reference to the respective chapter of Volume 2A is made.

To ensure smooth flow of the presentation, citing references will be avoided, which can be seen in the original publication.

3.5 Volume 2A—Chapter 1

This provides the general principles of the Union pharmaceutical legislation.

3.5.1 Marketing authorization

A medicinal product may only be placed on the market in the EEA when a marketing authorization has been issued:

- By the competent authority of a Member State for its own territory (national authorization);
- Or when an authorization has been granted for the entire Union (a Union authorization) in accordance with Regulation (EC) No. 726/2004.

3.5.2 National authorization

The competent authorities of the Member States are responsible for granting marketing

authorizations for medicinal products that are placed on their markets.

To obtain a national marketing authorization, an application must be submitted to the competent authority of the Member State.

However, and in cases where national authorizations are requested for the same medicinal product in more than one Member State and the MAH has received a marketing authorization in a Member State, the applicant/MAH must submit an application in the Concerned Member States (abbreviated CMS) using the procedure of mutual recognition (abbreviated MRP).

The Concerned Member States should then recognize the marketing authorization already granted by the Reference Member State (RMS) and authorize the marketing of the product on their national territory.

If no marketing authorization has been granted in the Union, the applicant may make use of a decentralized procedure (abbreviated DCP) and submit an application in all the Member States where it intends to obtain a marketing authorization at the same time and choose one of them as RMS.

Based on the assessment report prepared by the RMS and any comments made by the CMS, marketing authorization should be granted in accordance with the decision taken by the RMS and CMS in this decentralized procedure.

The marketing authorization must contain the summary of product characteristics (SmPC) according to Article 11 of Directive 2001/83/EC and the labeling and the package leaflet according to Articles 54, 55, 59, and 63 of Directive 2001/83/EC as amended.

3.5.3 Union authorizations

The Union will grant marketing authorizations for medicinal products:

- Referred to in the Annex to Regulation (EC) No. 726/2004, which may only be authorized via the centralized procedure (mandatory scope);
- Referred to in Article 3(2) of Regulation (EC) No. 726/2004, relating to products containing new active substances, products that constitute a significant therapeutic, scientific, or technical innovation, or products for which the granting of a Union authorization would be in the interest of patients or animal health at Union level;
- The applicant has to request confirmation that the product is eligible for evaluation through the centralized procedure (optional scope) and the EMA will decide on the matter;
- A generic medicinal product of a centrally authorized medicinal product if not using the option in Article 3(3) of Regulation (EC) No. 726/2004.

To obtain a Union authorization, an application must be submitted to the EMA. More details are provided in the original publication (Section 3.1 of Chapter 1 of Notice to Applicants).

Such a marketing authorization is valid throughout the Union and confers the same rights and obligations in each of the Member States as a marketing authorization granted by that Member State.

Once a central marketing authorization has been issued, the maintenance of existing national marketing authorization or the issuing of new national marketing authorizations for the same medicinal product could be envisaged only as long as the therapeutic indications are different in national and central marketing authorizations.

3.5.4 Notion of "global marketing authorization"

Based on Article 6(1) second subparagraph of Directive 2001/83/EC, the global marketing authorization contains the initial authorization and all variations and extensions thereof, as well as any additional strengths, pharmaceutical form, administration routes, or presentations authorized through separate procedures, including in different Member States within the

EU, and under a different name, granted to the MAH of the initial authorization.

Under this section, three different scenarios and notion of global marketing authorization are cited:

1. If the medicinal product being assessed contains a modification of an existing active substance, it should be clarified during the marketing authorization procedure whether the product contains a new active substance or not.
   If the assessment report does not indicate that the product contains a new active substance, it will be considered that the product at stake contains the same active substance and belongs to the global marketing authorization of the already authorized medicinal product(s) as described in Article 6(1) of Directive 2001/83/EC:
   Example: Active substance A in MP1 → Active substance A′ in MP2.
2. If the medicinal product being assessed contains within the same pharmaceutical form a combination of active substances, it will form a new and unique medicinal product requiring a separate marketing authorization, regardless of whether all of the active substances contained therein were already authorized in a medicinal product or not.
   The applicant must demonstrate that each active substance has a documented therapeutic contribution within the combination and therefore all compounds are different active substances.
   The authorization for this new combination medicinal product is not considered to fall within the scope of the global marketing authorizations of the already authorized medicinal product(s) as described in Article 6(1) of Directive 2001/83/EC.
   Examples:
   Active substance A in MP1, Active substance B in MP2 → Active substances A+B in MP3.
   Active substances A+B in MP1, Active substances C+D in MP2 → Active substances A+C in MP3.
   Active substances A+B in MP1, Active substance C in MP2 → Active substances A+C in MP3.
   Active substances A+B in MP1 → Active substance A+C in MP2.
3. If the medicinal product being assessed contains only one active substance, which was part of an authorized combination product, the new medicinal product will form a new and unique medicinal product requiring a separate marketing authorization.

The authorization for the new medicinal product is not considered to fall within the scope of the global marketing authorizations of the already authorized combination medicinal product as described in Article 6(1) of Directive 2001/83/EC.

Multiple applications of the same MAH are covered by the notion of "global marketing authorization."

3.5.5 Validity of the marketing authorization

3.5.5.1 Renewal

Marketing authorizations granted in the Union have an initial duration of 5 years. After these 5 years, the marketing authorization may be renewed on the basis of a reevaluation of the risk–benefit balance. To this end, the MAH must provide the EMA or the national competent authority with a consolidated version of the file in respect of quality, safety, and efficacy, including all variations introduced since the marketing authorization was granted, at least 9 months before the marketing authorization ceases to be valid. Once renewed, the marketing authorization is valid for an unlimited period unless the Commission or the national competent authority decides, on justified grounds relating to pharmacovigilance, to proceed with one additional 5-year renewal.

Recommendations regarding the content of the consolidated file for the renewal are provided in the EMA Guideline on the Processing of Renewals in the Centralised Procedure [18] and CMDh Best Practice Guide on the Processing of Renewals in the Mutual Recognition Procedure/Decentralized Procedure [19].

3.5.5.2 Cessation of the marketing authorization if the medicinal product is not marketed

Any authorization that within 3 years of its granting is not followed by the actual placing on the market of the authorized product in the authorizing Member State or on the Union market will cease to be valid.

Also, when an authorized product previously placed on the market in the authorizing Member State or in the Union is no longer actually present on the market for a period of 3 consecutive years, the authorization for that product will cease to be valid.

A medicinal product is "placed on the market" at the date of release into the distribution chain. It is the date when the product comes out of the control of the MAH.

For centrally authorized medicinal products, "placed on the Union market" means that the medicinal product is at least marketed in one Member State of the Union. For nationally authorized products "placed on the market in the authorizing Member State" means that the medicinal product is on the market of the Member State that has granted the marketing authorization. This is independent of the authorization procedure used (decentralized, mutual recognition, or purely national procedure).

After a marketing authorization has been granted, the holder of the authorization must inform the competent authority of the authorizing Member State or the EMA of the date of actual marketing of the medicinal product in that Member State or in the Union, considering the various presentations authorized.

The holder must also notify the national competent authority or the EMA if the product ceases to be placed on the market, either temporarily or permanently.

3.5.6 Naming of a medicinal product

The marketing authorization must contain the name of the medicinal product, which may be either an invented name, or a common or scientific name (when available, the international nonproprietary name of the active substance(s)) accompanied by a trade mark or the name of the MAH.

In the case of Union authorizations granted following applications through the centralized procedure, it is important that applicants identify at an early stage a name that would be valid throughout the Union when using the centralized procedure.

For applications through the mutual recognition and decentralized procedures, it is recommended whenever feasible that the same name for a given medicinal product should be used in all Member States. If a different name is to be used, it should be quoted in a covering letter from the applicant to the relevant competent authorities.

Where a generic of a medicinal product authorized through the centralized procedure is authorized by the competent authorities of the Member States, the generic medicinal product has to be authorized under the same name in all the Member States where the application has been made. For these purposes, all the linguistic versions of the international nonproprietary name are considered to be the same name (Article 3(3) of Regulation (EC) No. 726/2004).

3.5.7 Transparency

In accordance with Article 21 of Directive 2001/83/EC, the national competent authorities are obliged to make publicly available the decision granting the marketing authorization.

This decision is appended with the package leaflet, the SmPC, and any possible condition to the marketing authorization.

3.5.8 Multiple application

3.5.8.1 Centralized application

In the framework of the centralized procedure only one marketing authorization may be granted to an applicant for a specific medicinal product.

However, according to Article 82(1) second subparagraph of Regulation (EC) 726/2004 the same applicant can submit more than one application for the same medicinal product when there are objective verifiable reasons:

- Relating to public health regarding the availability of medicinal products to healthcare professionals and/or patients
  or
- For comarketing reasons.

In such case, the Commission will inform the applicant whether the conditions are met before he submits his application to the EMA.

3.5.8.2 Mutual recognition and decentralized procedures

There are no corresponding provisions in Directive 2001/83/EC that apply to these procedures.

However, to avoid submission of multiple applications in different Member States and handled outside, the principles of mutual recognition laid down in Chapter IV of Directive 2001/83/EC should be observed:

- Reference to any authorization obtained for that medicinal product should be provided with the application for a marketing authorization; as far as possible, the same RMS should be used in the case of multiple applications;
- Article 18 should be relied on to avoid multiple applications that are used to obtain marketing authorizations for the same medicinal product in different Member States outside the procedural framework of Chapter IV of Directive 2001/83/EC;
- The applicant may decide whether the mutual recognition procedure or the decentralized procedure is used for obtaining the multiple marketing authorizations.

See CMDh Recommendations on Multiple Applications in Mutual Recognition and Decentralised Procedures (June 2007) [20].

3.5.8.3 Concept of "applicant and marketing authorization holder"

An "applicant" and "marketing authorization holder" can be a physical or legal entity.

However, for the purposes of the application of the pharmaceutical rules, it is noted that:

- Applicants and MAHs belonging to the same company group or that are controlled by the same physical or legal entity are to be considered as one entity.
- Applicants and MAHs that do not belong to the same company group and are not controlled by the same physical or legal entity are to be considered as one applicant/MAH:
  - If they have concluded tacit or explicit agreements concerning the marketing of the same medicinal product for the purposes of the application of the pharmaceutical rules regarding that medicinal product.
  - This includes cases of joint marketing but also cases where one party licenses to the other party the right to market the same medicinal product in exchange for fees or other considerations.

From above, it is inferred the applicant and the marketing authorization holder are not necessarily of the same entity and could be of different companies. However as per the EU requirements both should have a proof of establishment in EEA and for this reason, most of the non-EU companies would have a representing office in EU.

3.6 Marketing authorization procedures

In addition to independent national procedure, in the EU there are three different procedures, namely:

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

3.6.1 Centralized procedure

In this procedure there are two possibilities:

1. Medicinal products that fall within the mandatory scope of the centralized procedure in accordance with the Annex to Regulation (EC) No. 726/2004, the application is submitted to the EMA.
2. Medicinal products that fall within the optional scope of the centralized procedure in accordance with Article 3(2) and 3(3) of Regulation (EC) No. 726/2004 where the applicant wishes to obtain a Union marketing authorization.

Following the scientific evaluation and upon receipt of the opinion, the EC drafts a decision on a Union marketing authorization and, after consulting the Standing Committee for Medicinal Products for Human Use, grants a marketing authorization.

3.6.2 Decentralized procedure and mutual recognition procedure

Both procedures are based on the recognition by national competent authority's assessment performed by the authorities of oneMember State.

According to the European Court of Justice, […]

> Article 28 of Directive 2001/83/EC […] confers a Member State in receipt of an application for mutual recognition only a very limited discretion in relation to the reasons for which that Member State is entitled to refuse to recognise the marketing authorisation in question. In particular, as regards any assessment going beyond the verification of the validity of the application with regard to the conditions laid down in Article 28, the Member State concerned, except where there is a risk to public health, must rely on the assessments and scientific evaluations carried out by the reference Member State. Although the facts of the case relate to a MRP, the ECJ is interpreting Article 28 (4) which applies both to MRP and DCP.

3.6.3 Decentralized procedure

For medicinal products not falling within the mandatory scope of the centralized procedure, the applicant may request one or more concerned Member State(s) to approve a draft assessment report, SmPC, and labeling and package leaflet as proposed by the chosen RMS. An application is submitted to the competent authorities of the RMS and the concerned Member State(s), together with the information and particulars referred to in Articles 8, 10, 10a, 10b, 10c, and 11 of Directive 2001/83/EC.

At the end of the decentralized procedure with a positive agreement, a national marketing authorization will be issued in the RMS and the concerned Member State.

3.6.4 Mutual recognition procedure

This procedure is based on the mutual recognition by concerned Member State(s) of a national marketing authorization granted by the RMS.

At the end of the mutual recognition procedure, a national marketing authorization will be issued in the concerned Member State(s).

3.6.5 Independent national procedures

These procedures will apply to medicinal products that are not to be authorized in more than one Member State.

3.7 Paediatric requirements for medicinal products

Regulation (EC) No. 1901/200620 of the European Parliament and of the Council on Medicinal Products for Paediatric Use entered into force on January 26, 2007.

It aims to facilitate the development and availability of medicinal products for use in the paediatric population.

To attain this goal, the regulation places on applicants certain obligations, the main one being submission of data on the use of a medicinal product in children obtained in accordance with an agreed PIP by the EMA. Provided that the requirements of Regulation 1901/2006 are fulfilled, the applicants may then be eligible for a reward, as provided in Title V of this Regulation,

that may be an extension of the supplementary protection certificate, extension of market exclusivity, or data/market protection, as the case may be.

Information on guidelines developed by the CMDh are given on the website [21].

3.8 Union referrals

In certain circumstances in the framework of marketing authorizations granted by the competent authorities of the Member States, a Union procedure, involving a scientific opinion by, as appropriate, the CHMP/PRAC, can be triggered. This procedure is commonly called Union "referral," which may be triggered in the cases listed in the following.

3.8.1 Referral according to Article 29 of Directive 2001/83/EC

Where one or more concerned Member States cannot agree on the recognition of an authorization already granted in a mutual recognition procedure or a final assessment and product information prepared by the RMS in view of granting the marketing authorization in a decentralized procedure due to a potential serious risk to public health.

The points of disagreement must be referred to the coordination group provided by Article 27 of that Directive.

Where the Member States concerned by the procedure fail to reach an agreement within the coordination group, the matter is referred to the CHMP for application of the procedure laid down in Articles 32–34 of Directive 2001/83/EC.

This referral is automatic in the sense that, once a Member State has raised a concern on the grounds of potential serious risk to public health within the meaning of Article 29(1), withdrawal of the marketing authorization application in that Member State does not prevent the concern from being analyzed within the coordination group and, in the absence of an agreement therein, the EMA.

The expression "potential serious risk to public health" is defined in the Commission's Guideline on the definition of a potential serious risk to public health in the context of Article 29(1) and (2) of Directive 2001/83/EC [22].

3.8.2 Referral in accordance with Article 30(1) of Directive 2001/83/EC

If two or more applications submitted in accordance with Articles 8, 10, 10a, 10b, 10c, and 11 of that Directive have been made for marketing authorization for a particular medicinal product, and if Member States have adopted divergent decisions concerning the authorization of the medicinal product or its suspension or revocation, a Member State, the Commission, applicant, or the MAH may refer the matter to the CHMP.

3.8.3 Referral in accordance with Article 30(2) of Directive 2001/83/EC

To promote harmonization of authorizations for medicinal products authorized in the Union, Member States must, each year, forward to the coordination group a list of medicinal products for which a harmonized SmPC should be drawn up. The coordination group must lay down a list considering the proposals from all Member States and will forward this list to the Commission. The Commission or a Member State, in agreement with the Agency and considering the views of interested parties, may refer these products to the committee.

3.8.4 Referral in accordance with Article 31 of Directive 2001/83/EC

The Member States or the Commission or the applicant or the MAH must, in specific cases where the interests of the Union are involved, refer the matter to the committee for the application of the procedure laid down in Articles 32, 33, and 34 before any decision is reached on a request for a marketing authorization or on the suspension or revocation of an authorization, or any other variation to the terms of a marketing authorization that appears necessary.

Where the referral results from the evaluation of data relating to pharmacovigilance the matter must be referred to the PRAC. Its final

recommendation will be forwarded to the CHMP or the coordination group, as appropriate.

However, when one of the criteria listed in Article 107i(1) is met, the procedure laid down in Articles 107i–107k must apply.

Where the referral concerns a range of medicinal products or a therapeutic class, the Agency may limit the procedure to specific parts of the authorization.

In such a case, Article 35 must apply to those medicinal products only if they were covered by the authorization procedures referred to in this chapter (decentralized and mutual recognition procedures).

3.8.5 Referral in accordance with Article 107i of directive 2001/83/EC

A Member State or the Commission, as appropriate, must, on the basis of concerns resulting from the evaluation of data from pharmacovigilance activities:

(a) Initiate the procedure provided for in the section by informing the other Member States, the Agency, and the Commission where it considers suspending or revoking a marketing authorization, prohibiting the supply of a medicinal product, refusing the renewal of a marketing authorization, or it is informed that the MAH, on the basis of safety concerns, has interrupted the placing on the market of a medicinal product or has taken action to have a marketing authorization withdrawn, or intends to take such action or has not applied for the renewal of a marketing authorization.

(b) Inform the other Member States, the Agency, and the Commission where it considers that a new contraindication, a reduction in the recommended dose or a restriction to the indications of a medicinal product is necessary. The information must outline the action considered and the reasons therefor.

(c) Initiate the procedure in any of the cases referred in the paragraph (b), when urgent action is considered necessary.

3.9 Application types

The legal requirements and the procedures for making an application for a marketing authorization in European Union are set out in Directive 2001/83/EC and in regulation (EC) No. 726/2004, which are briefly highlighted in the early part of this Chapter. A brief description of these legal requirements and procedures is set out in this chapter for applications according to:

- Article 8(3) of Directive 2001/83/EC
- Article 10 of Directive 2001/83/EC, relates to generic medicinal products, "hybrid" medicinal products, and similar biological medicinal products;
- Article 10a of Directive 2001/83/EC, relates to applications relying on well-established medicinal use supported by bibliographic literature;
- Article 10b of Directive 2001/83/EC, relates to applications for new fixed combinations of active substances in a medicinal product;
- Article 10c of Directive 2001/83/EC, relates to informed consent from an MAH for an authorized medicinal product.

3.9.1 Applications according to Article 8(3) of Directive 2001/83/EC

An application for marketing authorization must be accompanied by the particulars and documents set out in Article 8(3) of Directive 2001/83/EC and therefore the following documentation must be included in the dossier:

- Pharmaceutical (physicochemical, biological, or microbiological) tests;
- Preclinical (toxicological and pharmacological) tests;
- Clinical trials.

For such applications, the relevant published literature also has to be submitted and these scientific publications can be used as supportive data.

Types and details of the studies included in each of the three tests are detailed in Volume 2B of the Notice to Applicants [23].

It provides guidance to the compilation of the dossiers for application for EU marketing authorization applicable for the centralized and national procedures, including mutual recognition and decentralized procedures. Further details about these procedures are explained in this section.

Volume 2B of Notice to Applicants takes account of the international agreement on the structure and format of the common technical document (CTD), which were agreed in November 2000 within the International Conference on Harmonisation (ICH) framework and further documents and guidelines agreed upon since that time.

More details about ICH and guidelines are given on the ICH website [24].

For a quick view of the content of the CTD, a schematic pyramid used by the ICH and EU websites is presented in Fig. 3.3.

It is beyond the scope of this section to discuss the details and content of the dossier but it can be seen under Volume 2B of the Notice to Applicants mentioned earlier.

Of special interest, within module 5 of the CTD, and for clinical trials carried outside the EU, a statement to that effect confirming the compliance to the ethical requirements of Directive 2001/20/EC should be submitted.

Furthermore, in the "Guideline on the Investigation of Bioequivalence, 2010" [25], bioequivalence trials conducted in the EU/EEA have to be carried out in accordance with Directive 2001/20/EC. Trials conducted outside the Union and intended for use in a marketing authorization application in the EU/EEA have to be conducted to the standards set out in Annex I of the Community Code, Directive 2001/83/EC as amended.

3.9.2 Applications according to Article 10 of Directive 2001/83/EC

3.9.2.1 Reference medicinal product

Reference can be made to the dossier of a reference medicinal product for which a marketing authorization has been granted in the Union

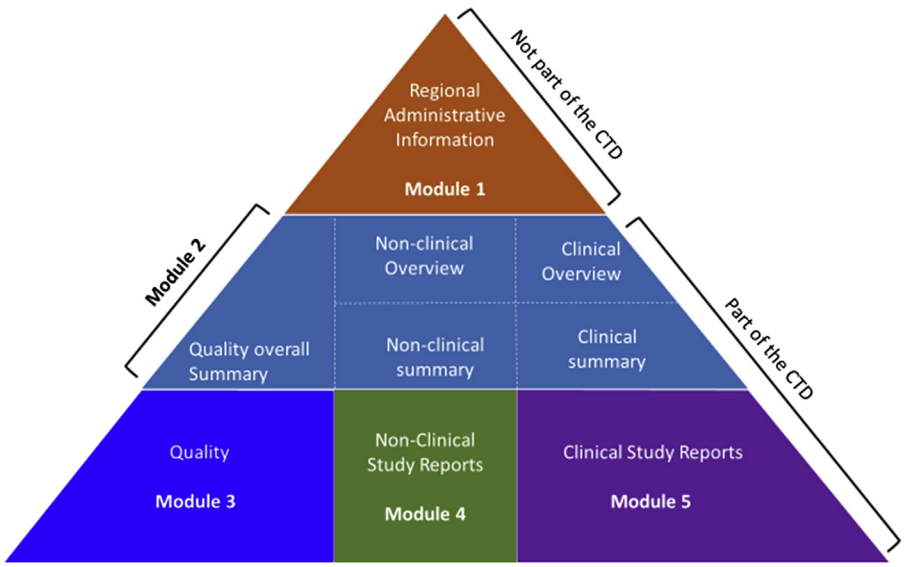

FIGURE 3.3 The common technical document (CTD) triangle. Module 1 is region specific and modules 2, 3, 4, and 5 are intended to be common for all regions.

in accordance with Articles 8(3), 10a, 10b, or 10c of Directive 2001/83/EC.

The application form in module 1 of the dossier for an Article 10 application should clearly identify the reference product in order for the RMS, in case of mutual recognition procedure/decentralized procedure, to prepare the assessment report.

Each product within the global marketing authorization may be chosen as the reference medicinal product.

Reference cannot be made to the dossier of a medicinal product for which a marketing authorization has been granted in the Union in accordance with Article 10(1).

Data supporting applications approved under Article 10(3) (e.g., new indications, strength, route of administration, pharmaceutical form) do not benefit from periods of exclusivity.

As an exception, when specifically provided for new therapeutic indications based on Article 10(5).

For example, Product B (Company 2) was approved according to Article 10(3) based on additional preclinical and/or clinical studies (e.g., supporting a new indication, strength, pharmaceutical form, or route of administration) to those submitted in support of the reference product (Product A, Company 1). A subsequent application may be submitted for Product C (Company 3), which refers to data supporting the reference product (Product A) and also to the data submitted in support of Product B (approved according to Article 10(3)), provided that any data exclusivity awarded in respect of a possible new therapeutic indication for Product B has elapsed. The application for Product C may be accepted irrespective of whether Products A and B belong to the same global marketing authorization. In such a case, Product A would be the reference medicinal product in support of the application for Product C.

Applicants proposing such a marketing authorization application are advised to contact the competent authorities in advance of the submission.

Reference must be made to a product that is or has been authorized in the Union (i.e., a marketing authorization has been granted for the reference medicinal product, but it may have ceased to exist).

In case, the reference medicinal product is no longer produced and placed in the Union market; demonstration of the bioequivalence with the reference medicinal product through bioavailability studies should, however, be performed on batches that have been authorized within the Union.

Authorizations for generic medicinal products are linked to the "original" authorization. This does not, however, mean that withdrawal of the authorization for the reference product leads to withdrawal of the authorization for the generic product.

An application according to Article 10 of Directive 2001/83/EC cannot be filed simultaneously with an application for a reference product.

The MAH of the reference medicinal product can file an application on the basis of Article 10 to his/her own medicinal product, provided that the requirements of Article 10 are fulfilled, for example, the data exclusivity period has expired.

3.9.2.2 European reference medicinal product

According to Article 10(1) third subparagraph of Directive 2001/83/EC, a generic application can also be submitted in a Member State although the reference medicinal product has never been authorized in that Member State. In that case, a reference medicinal product in another Member State should be identified, a so-called European reference medicinal product.

In these cases, the applicant has to identify in the application form the name of the Member State in which the reference medicinal product is or has been authorized. It is also a prerequisite that the period of data exclusivity has expired in the Member State of the reference medicinal product.

At the request of the competent authority of the Member State in which the application is submitted, the competent authority of the other Member State should transmit, within a period of 1 month, a confirmation that the reference medicinal product is or has been authorized together with the full composition of the reference product and if necessary other relevant documentation.

3.9.2.3 Particularities for application according to Article 10

Article 10 constitutes a single legal base for the submission of applications. The content of such applications must comply with the requirements set out therein.

Directive 2001/83/EC defines a generic medicinal product in Article 10(2)(b) as a medicinal product that has:

- The same qualitative and quantitative composition in active substances as the reference medicinal product.
  This requirement extends only to the active substance(s) and not to the other ingredients of the product. However, differences in excipient composition or differences in impurities must not lead to significant differences as regards safety and efficacy:
  The different salts, esters, ethers, isomers, mixtures of isomers, complexes, or derivatives of an active substance must be considered to be the same active substance, unless they differ significantly in properties with regard to safety and/or efficacy.
- The same pharmaceutical form as the reference medicinal product,
  A generic product and a reference product may be considered to have the same pharmaceutical form if they have the same form of administration as defined by the Pharmacopoeia.
  Furthermore, the various immediate release oral forms, which would include tablets, capsules, oral solutions, and suspensions, are considered to be the same pharmaceutical form for the purposes of Article 10:
- and whose bioequivalence with the reference medicinal product has been demonstrated by appropriate bioavailability studies. Bioavailability studies need not be required if the applicant can demonstrate that the generic medicinal product meets the relevant criteria as defined in the detailed guideline on the investigation of bioequivalence.

Where bioequivalence cannot be demonstrated through bioavailability studies, Article 10(3) requires that the results of appropriate preclinical tests or clinical trials will be provided.

3.9.2.4 Applications in accordance with paragraph 3 of Article 10 ("hybrid medicinal product")

In certain circumstances in the framework of an application under Article 10, the results of the appropriate preclinical tests or clinical trials shall be provided.

These applications will thus rely in part on the results of preclinical tests and clinical trials for a reference product and in part on new data.

The extent of the additional studies required in the framework of an Article 10(3) application depends on the changes introduced vis-à-vis the reference medicinal product (e.g., new strength, new route of administration, new therapeutic indication) and will be a matter of scientific assessment by the relevant competent authority.

Article 10(3) considers three circumstances where such additional data will be necessary:

- Where the strict definition of a "generic medicinal product" is not met. Some examples and requirements are given under Section 3.12 at the end of the chapter.
- Where bioavailability studies cannot be used to demonstrate bioequivalence (for example, where the new product is for locally applied/locally acting medicinal products). Therapeutic equivalence (safety/efficacy) of the generic product compared to the

reference product should be demonstrated (cf. guideline).
- Where there are changes in the active substance(s), therapeutic indications, strength (outside the current approved range), pharmaceutical form, or route of admini-stration of the generic product compared to the reference product, clinical/bioavailability studies would be required.

3.9.2.5 Applications according to Article 10a of Directive 2001/83/EC

According to this article, it is possible to replace results of the preclinical and clinical trials with detailed references to published scientific literature if it can be demonstrated that the active substances of a medicinal product in the claimed therapeutic indication have been in well-established medicinal use within the Union for at least 10 years, with recognized efficacy and an acceptable level of safety.

The adequacy of the bibliographic evidence has to be assessed on a case-by-case basis in the understanding that applications under Article 10a do not lower the requirements of safety and efficacy that must be met.

3.9.2.6 Well-established medicinal use

Annex I of Directive 2001/83/EC lays down specific rules for the demonstration of a well-established medicinal use, with recognized efficacy and an acceptable level of safety.

The following criteria should be considered:

- The time over which a substance has been used with regular application in patients; quantitative aspects of the use of the substance, considering the extent to which the substance has been used in practice, the extent of use on a geographical basis, and the extent to which the use of the substance has been monitored by pharmacovigilance or other methods;
- The degree of scientific interest in the use of the substance (reflected in the published scientific literature) and the coherence of scientific assessments.

The period of time required for establishing a well-established medicinal use of a constituent of a medicinal product must not be less than one - decade from the first systematic and documented use of that substance as a medicinal product in the Union.

Well-established use refers to the use for a specific therapeutic use. If well-known substances are used for entirely new therapeutic indications and it is not possible to solely refer to a well-established use, then additional data on the new therapeutic indication together with appropriate preclinical and human safety and/or efficacy data should be provided. In such a case, another legal basis should be used for the marketing authorization application.

Marketing authorization applications for fixed combinations intended to be used in patients who are already stabilized on optimal doses of the combination of the same, but separately administered active substances, taken at the same dose interval and time, can be submitted on the basis of Article 10a.

In such cases, the detailed references to published scientific literature submitted must concern the systematic and documented use of the active substances in combination.

It is nevertheless possible to include information on the individual active substances in the application. This will typically occur where the applicant intends to justify the absence of certain specific data on the combination by reference to the information available on the individual substances. A product approved under Article 10a can act as a Reference Medicinal Product for a subsequent Article 10 application as they have been approved under a full dossier and data exclusivity/market protection periods of 10 years would apply. From a legal perspective, a generic to a reference medicinal product which had been licensed under Article 8(3)(ia) can also claim well established use (WEU) once the 10 years of

exclusivity elapsed. The difference is that in 10.1 application reference to a reference medicinal product should be made supported by bioequivalence study or its absence should be justified under the biowaiver regulation. However, in 10a application reference to a reference medicine (approved for more than 10 years) would not be required and efficacy and safety of the product can be claimed through scientific literature survey and citation. Because of this possibility, to the acceptance of the competent authority, the claim for WEU should be well justified.

3.9.2.7 Documentation

The applicant should provide a detailed description of the strategy used for the search of published literature and the justification for inclusion of references in the application. The reference must be made to "published scientific literature." The term "published" literature implies that the text must be freely available in the public domain and published by a reputable source, preferably peer reviewed.

All documentation, both favorable and unfavorable, should be communicated. If documentation is lacking, a justification should be given. If parts of the dossier are incomplete, particular attention must be paid to explain why in the overall overview/summaries.

When compiling published scientific literature, applicants should also include postmarketing experience with medicinal products containing the same active substance.

Copies of the full text of the literature, including necessary translations, must be submitted.

3.9.2.8 Applications according to Article 10b of Directive 2001/83/EEC

The combination of active substances within a single pharmaceutical form of administration according to this provision is a so-called "fixed combination."

A key principle of the *acquis* is that there must be a marketing authorization for each medicinal product that is put on the EU market. Therefore the fixed combination definition is limited to active substances contained in a same pharmaceutical form of administration, the so-called "fixed combination."

The combination of active substances, where active substances are included in separate pharmaceutical forms and presented in a combination pack, cannot be considered as fixed combination.

In the case of an application on the basis of Article 10b of Directive 2001/83/EC, the applicant does not have to provide scientific references relating to each individual active substance.

Applications for fixed combination medicinal products under Article 10b are conditioned to the fact that the individual substances have been the object of a marketing authorization in the EEA via a Union or national procedure, even though it is not in the same Member State.

In case the dossier is only composed of references to published scientific literature, the legal basis would not be Article 10b of Directive 2001/83/EC, but possibly 10a if all requirements are fulfilled.

3.9.2.9 Applications according to Article 10c of Directive 2001/83 /EC

A derogation from the requirements to submit all of the information required in Article 8(3)(i) is provided by Article 10c of Directive 2001/83/EC for so-called "informed consent" marketing authorization applications.

Despite the fact that the provision contains criteria that are common to the definition of a generic medicinal product in Article 10, Article 10c does not concern generic medicinal products.

An informed consent application does not have to cover all presentations/indications of the medicinal product with regard to which consent is given. Consent may be given to use the documentation contained in the file of the relevant medicinal product for a given presentation/indication provided that the application

relies on that consent as regards all three modules of the dossier.

It is a prerequisite for the use of Article 10c that consent has been obtained for all three modules containing the pharmaceutical, preclinical, and clinical data. It is not possible to use Article 10c as a legal basis for an application consisting of the applicant's own module 3 and for which consent has been given for modules 4 and 5. In such cases the legal basis for the application is Article 8(3).

An informed consent application cannot cover more presentations or indications than the medicinal product with regard to which consent is given.

The concept of "European reference medicinal product" is laid down by Article 10 and is applicable in case of application in accordance with Article 10. It does not apply in the context of applications under Article 10c.

In addition, it should be noted that an informed consent application is only possible if there is still a valid marketing authorization to which consent is given.

Furthermore, informed consent applications need to respect the following:

- For a central marketing authorization, the informed consent application has to follow the centralized procedure;
- For a national marketing authorization, the informed consent application has to follow a national procedure (either pure national or mutual recognition procedure or decentralized procedure). A prerequisite is that the marketing authorization is granted in this/these Member State(s).

It follows that an application under Article 10c can only be submitted to a Member State where the medicinal product with regard to which consent is given is authorized.

The applicant must show proof that the MAH of the reference product has consented that the dossier of that product is used for the purpose of examining the application in question.

The "informed consent" product applicant must have permanent access to the documentation to fully carry out his responsibilities. For the information contained in the Active Substance Master File a new letter of access in connection with the informed consent application should be included, without prejudice to the restrictions on access to the Manufacturer Restricted Part of the Active Substance Master File. Nevertheless, in UK only and not in any other EU member state, it is permissible to duplicate the license of a generic medicinal product conditional to be issued to another company not linked to the MAH.

3.10 Data exclusivity and market protection

This subject is more legal than technical, and the reader is recommended to seek legal advice on this subject prior to submission to ensure compliance. However, in this chapter a very short description of the main points that are of relevance to the regulatory affair and dossier submission is briefly made:

The medicinal product, once authorized on the basis of Article 10, can, however, only be placed on the market 10 or 11 years after the authorization of the reference medicinal product, depending on the protection period applicable for the reference medicinal product. The protection period in the concerned Member State must also be taken into consideration before placing the medicinal product on its market.

For products authorized by the national competent authorities, according to the first subparagraph of Article 10(1) of Directive 2001/83/EC as amended by Directive 2004/27/EC, the applicant is not required to provide the results of preclinical tests and of clinical trials if he can demonstrate that the medicinal product is a generic of a reference medicinal product that is or has been authorized under Article 6 for not less than 8 years in a Member State or in the Union.

According to the second subparagraph of Article 10(1), generic products authorized in this way must not be placed on the market until 10 years have elapsed from the initial authorization of the reference product.

The period of 8 years from initial authorization of the reference product provides a period of so-called "data exclusivity," after which valid applications for generic products can be submitted and lead to the granting of a marketing authorization.

The period of 10 years from initial authorization of the reference product provides a period of so-called "market protection" after which generic products authorized in this way can be placed on the market.

The same periods of protection apply in the case of centrally authorized products pursuant to Article 14(11) of Regulation (EC) No. 726/2004.

3.10.1 Protection periods and global marketing authorization

For the notion of global marketing authorization, see Section 2.3. Global marketing authorization contains the initial authorization and all variations and extensions thereof, as well as any additional strengths, pharmaceutical form, administration routes, or presentations authorized through separate procedures and under a different name, granted to the MAH of the initial authorization. In accordance with Article 6(1) of Directive 2001/83/EC, all these presentations of a given product are considered to be part of the same marketing authorization for the purposes of applying the rules on data exclusivity and marketing protection. This means that for a reference medicinal product, the start of the data exclusivity and market protection periods is the date when the first marketing authorization was granted in the Union in accordance with the pharmaceutical *acquis*. New additional strengths, pharmaceutical form, administration routes, presentations, as well as any variation and extensions do not restart or prolong this period. All additional strengths, pharmaceutical form, administration routes, presentations, as well as any variation and extensions have the same end point of the data exclusivity and market protection periods, namely 8 and 10 years after the first marketing authorization was granted, respectively. This will apply even if the new presentation has been authorized to the same MAH through a separate procedure, national or centralized procedure, irrespective of the legal basis and under a different name.

This 10-year period can only be prolonged in the case of certain new indications.

3.10.1.1 Extension of the 10-year period in Article 10(1) in the case of new therapeutic indications

In accordance with the fourth subparagraph of Article 10(1) of Directive 2001/83/EC, the 10-year period of marketing protection may be extended by 1 year in the event of authorization of new therapeutic indications representing a significant clinical benefit in comparison with existing therapies.

The additional year of marketing protection applies to the global marketing authorization for the reference medicinal product. Generic products, with or without the new therapeutic indication, may not be placed on the market until expiry of the 11th year.

To benefit from the additional year, the new indication must be approved during the first 8 years since the initial marketing authorization has been granted. The overall period of protection cannot exceed 11 years. Therefore this provision can be used only once per "global marketing authorization" within the meaning of Article 6(1) of Directive 2001/83/EC.

Guidance on elements required to support the significant benefit in comparison with existing therapies of a new therapeutic indication to benefit from an extended (11 years) marketing protection period is available [26].

3.10.1.2 One-year period of protection for new indications of well-established substances

Article 10(5) of Directive 2001/83/EC reads: "In addition to the provisions laid down in

paragraph 1, where an application is made for a new indication for a well-established substance, a non-cumulative period of one year of data exclusivity will be granted, provided that significant pre-clinical or clinical studies were carried out in relation to the new indication."

An applicant referring to Article 10(5) must provide justification regarding the existence of a new indication, of a well-established substance, and of significant preclinical or clinical studies. The new indication can be included either in the existing marketing authorization via a Type II variation or submitted with an application for a new marketing authorization.

The data exclusivity period is noncumulative to other periods of protection: it refers exclusively to the data concerning the new indications. Therefore the concerned medicinal product could be used as reference medicinal product with the exclusion of the indication(s), which is covered by this data exclusivity if the medicinal product fulfills the general requirements of reference medicinal product.

Such data exclusivity period is an incentive for development of new indications, while data protection would not otherwise apply.

Guidance on a new therapeutic indication for a well-established substance is available [27].

3.10.1.3 One-year period of protection for data supporting a change of classification

Article 74a of Directive 2001/83/EC reads: "Where a change of classification of a medicinal product has been authorised on the basis of significant pre-clinical tests or clinical trials, the competent authority shall not refer to the results of those tests or trials when examining an application by another applicant for or holder of marketing authorisation for a change of classification of the same substance for one year after the initial change was authorised."

For further guidance please refer to the Guideline on Changing the Classification for the Supply of a Medicinal Product for Human Use, available at [28].

3.11 Variations and extensions

3.11.1 Variations

Throughout the life of a medicinal product, the MAH is responsible for the product that is placed on the market.

The MAH is required to consider technical and scientific progress, and to make any amendments/variations that may be required to ensure quality and compliance with the current requirements.

Such variations may involve changes to the product information or changes to the technical dossier initially submitted.

The procedures for the approval of variations have been set out in Commission Regulation (EC) No. 1234/2008 [29] concerning the examination of variations to the terms of marketing authorizations for medicinal products for human use and veterinary medicinal products. It has been amended by Regulation (EU) 712/2012) [30].

In accordance with Article 4(1) of the Variations Regulation, guidelines on the details of the various categories of variations, on the operation procedures laid down in Chapters II, IIa, III, and IV of that Regulation, as well as on the documentation to be submitted pursuant to these procedures were drawn by the EC.

These guidelines are intended to facilitate the interpretation and application of the Variations Regulation. They provide details on the application of the relevant procedures, including a description of all the relevant steps from the submission of an application for a variation to the final outcome of the procedure on the application.

The following categories of variations, defined in Article 2 of the Variations Regulation, are defined:

- Minor variations of Type IA
- Minor variations of Type IB
- Major variations of Type II
- Extensions
- Urgent safety restriction

Only the EC and the EMA, respectively, are responsible for any variations relating to centrally authorized products.

In the case of medicinal products for human use, the introduction of changes to the labeling or package leaflet that is not connected with the SmPC is not governed by the procedures of the Variations Regulation.

In accordance with Article 61(3) of Directive 2001/83/EC, these changes are to be notified to the relevant competent authorities and they may be implemented if the competent authority has not objected within 90 days.

It must be noticed that where a group of variations consists of different types of variations, the group must be submitted and will be handled according to the "highest" variation type included in the group. For instance, a group consisting of an extension and a major variation of Type II will be handled as an extension application; a group consisting of minor variations of Type IB and Type IA will be handled as a Type IB notification.

The application form for variations to a marketing authorization for medicinal products (human and veterinary) is available online [31].

The conditions and requirements for submission for each of these categorized variations are very different, so are the timetable and procedures governing the assessment and notification of the outcome. Providing details is avoided and the following is a brief description of the type of variations.

3.11.1.1 Minor variations of Type IA

Such minor variations do not require any prior approval but must be notified by the holder within 12 months following implementation ("Do and Tell" procedure).

A list of changes to be considered as minor variations of Type IA and the conditions that must be met for a change to follow a Type IA notification procedure are set out in the Variations Regulation and the annex to these guidelines. However, certain minor variations of Type IA require immediate notification after implementation to ensure the continuous supervision of the medicinal product.

Minor variations of Type IA do not require prior examination by the authorities before they can be implemented by the holder.

The holder may group several minor variations of Type IA under a single notification, as established in Articles 7(2) and 13d(2) of the Variations Regulation. Specifically, two possibilities exist for the grouping of variations of Type IA:

1. The holder may group several minor variations of Type IA regarding the terms of one single marketing authorization provided that they are notified at the same time to the same relevant authority.
2. The holder may group one or more minor variations of Type IA to the terms of several marketing authorizations under a single notification provided that the variations are the same for all marketing authorizations concerned and they are notified at the same time to the same relevant authority.

Review of Type IA will be carried out within 30 days following receipt by the RMS for mutual recognition procedure or by the national competent authority for purely national procedure.

By day 30, the national competent authority will inform the holder of the outcome of its review.

Where one or several minor variations of Type IA are submitted as part of one notification, the RMS/the national competent authority will inform the holder as to which variation(s) have been accepted or rejected following its review. The MAH must not implement the rejected variation(s).

The same rule will apply for a Type IA variation review for a centralized procedure, carried out by the Agency without involvement of the rapporteur.

3.11.1.2 Minor variations of Type IB

Such minor variations must be notified before implementation. The holder must wait a period of 30 days to ensure that the notification is deemed acceptable by the relevant authorities before implementing the change ("Tell, Wait and Do" procedure).

Within 30 days following the acknowledgment of receipt of a valid notification, the RMS/national competent authority will notify the holder of the outcome of the procedure. If the RMS/national competent authority has not sent the holder its opinion on the notification within 30 days following the acknowledgment of receipt of a valid notification, the notification will be deemed acceptable.

3.11.1.3 Major variations of Type II

Such major variations require approval of the relevant competent authority before implementation.

As a general rule, for major variations of Type II, a 60-day evaluation period will apply.

This period may be reduced by the national competent authority having regard to the urgency of the matter, particularly for safety issues, or may be extended to 90 days for variations listed in Part I of Annex V or for grouping of variations in accordance with Article 13d(2)(c) of the Variations Regulation.

Within the evaluation period, the RMS/national competent authority may request the holder to provide supplementary information. The request for supplementary information will be sent to the holder together with a timetable stating the date by when the holder should submit the requested data and where appropriate the extended evaluation period.

The procedure will be suspended until the receipt of the supplementary information. As a general rule, a suspension of 1 month will apply. For longer suspension the holder should send a justified request to the national competent authority for agreement.

The evaluation of responses may take up to 30 or 60 days depending on the complexity and amount of data requested to the holder.

The same rules will apply to Type II variations assessment for a centralized procedure.

For the outcome, slight differences in procedure of notification between the national procedure, mutual recognition procedure, and centralized procedure exist. The procedure and time permitted in implementing these outcomes would follow different routes given the involvement of other Member States in the mutual recognition procedure/centralized application compared to one authority in the case of a nationally approved application.

General rules apply to minor variations Type IB or major variations Type II:

1. Where the same minor variation of Type IB or the same group of minor variations or the same major variation of Type II or the same group of variations (as explained earlier) affect several marketing authorizations owned by the same holder, the holder may submit these variations as one application for "Worksharing."
   Details about applications for "Worksharing" and procedure are given in the original guideline and would not be covered on this occasion.
2. Holders may group under a single notification the submission of several variations regarding the same marketing authorization, or group the submission of one or more major variation(s) of Type II with other minor variations regarding the same marketing authorization, provided that this corresponds to one of the cases listed in Annex III of the Variations Regulation, or when this has been agreed previously with the RMS, the national competent authority, or the Agency (as appropriate).

3.12 Extensions

An extension to or a modification of the existing marketing authorization will have to be granted by the Community.

As established in Article 19 of the Variations Regulation (EC No. 1234/2008), such applications will be evaluated in accordance with the same procedure as for the granting of the initial marketing authorization to which it relates. The extension can either be granted as a new marketing authorization or will be included in the initial marketing authorization to which it relates. Annex I of the Variations Regulation sets out a list of changes to be considered as extensions. The following is a summary:

1. Changes to the active substance(s) include:
   - **(a)** Replacement of the active substance(s) by a different salt/ester complex/derivative (with the same therapeutic moiety) where the efficacy/safety characteristics are not significantly different;
   - **(b)** Replacement by a different isomer, a different mixture of isomers, or a mixture by an isolated isomer (e.g., racemate by a single enantiomer) where the efficacy/safety characteristics are not significantly different;
   - **(c)** Replacement of a biological substance or product of biotechnology with one of a slightly different molecular structure. Modification of the vector used to produce the antigen/source material, including a new master cell bank from a different source where the efficacy/safety characteristics are not significantly different;
   - **(d)** A new ligand or coupling mechanism for a radiopharmaceutical;
   - **(e)** Change to the extraction solvent or the ratio of herbal drug to herbal drug preparation where the efficacy/safety characteristics are not significantly different.

   Evidence to confirm that no change in the pharmacokinetics/pharmacodynamics and/or toxicity, which could significantly change the safety/efficacy profile, should be provided; Otherwise to be considered as a new active substance.
2. Changes to strength, pharmaceutical form, and route of administration include:
   - **(a)** Change of bioavailability;
   - **(b)** Change of pharmacokinetics, e.g., change in rate of release;
   - **(c)** Change or addition of a new strength/potency;
   - **(d)** Change or addition of a new pharmaceutical form;
   - **(e)** Change or addition of a new route of administration.

Clinical data (safety/efficacy), pharmacokinetics, preclinical (e.g., local toxicology), if justified, including bioavailability studies, might need to be provided.

Furthermore, on a case-by-case basis, biowaiver may be considered.

Extension applications must be submitted to all Member States concerned, to the national competent authority, or to the Agency (as appropriate).

4. Conclusion

The legal frame work covering the requirements and eligibility for marketing authorization of medicinal products in EU, ensuring compliance with the current EU standard for quality, safety and efficacy is well set out. In this chapter introduction to the Article, and regulations issued by the EU along with supporting publications explaining the legal requirements and procedures followed and how can they be implemented is made. This will help regulatory affair and technical professionals to determine the strategy of registration and market

penetration of medicinal product into different countries of EU and ways of achieving their goals. Regarding procedures, the decentralized route is the most common, whereby marketing authorization of the same medicinal product in more than one EU country at the same time through one procedure and one application can be made. Procedure for national application is still followed by some applicants for certain marketing strategy with option of mutual recognition into other EU countries once registered. This will take longer time to achieve compared to the decentralized procedure. However these different options are still applicable and available, providing the required flexibility for the applicants to follow.

Acknowledgments

As this chapter describes regulatory and legal rules. The language must be same as describes by authorization bodies. Therefore, I would like to acknowledge EMA and other regulatory bodies for the information stated on respective websites for public knowledge. Readers are requested to check latest updates in rules and regulations before preparing application.

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